CUK-H00b1A-64-P25690

ISSN 0006-8950

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Brain

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A JOURNAL OF NEUROLOGY

VOLUME 107 · PART III · SEPTEMBER 1984

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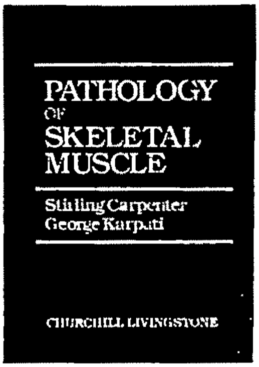

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TOPOGRAPHICAL ANATOMY OF THE POSTERIOR COLUMNS OF THE SPINAL CORD IN MAN

THE LONG ASCENDING FIBRES

by MARION C. SMITH *and* PATRICIA DEACON

(*From the Neuropathological Laboratory, Radcliffe Infirmary, Oxford OX2 6HE*)

SUMMARY

Nine cases are presented which illustrate the segmental anatomy of the posterior columns with respect to the long ascending fibres. It is concluded that the fasciculus gracilis (FG) and the fasciculus cuneatus (FC) should be considered as separate anatomical entities. It is shown that the shape of each fasciculus is different in, and characteristic of, each of the upper thoracic and cervical segments. A certain degree of segmental lamination is present in the FG, but with extensive overlapping of fibres from different segments. The orientation of the laminae is not the same in all segments, being very approximately parallel to the medial border of the posterior horn in most caudal segments, approximately parallel to the median septum in intermediate segments, and oblique in an anteromedial posterolateral direction in cranial sections. The pattern of lamination in the FC and the degree of overlapping of fibres resembles that in the caudal FG. There is no, or minimal, overlapping of fibres of the FC with those of the FG. The most medial fibres of the FC, lying along the lateral border of the FG, are in proximity with fibres, in that fasciculus, from many different segments.

INTRODUCTION

The traditional concept of the anatomy of the long ascending fibres in the posterior columns is a simple one of a parallel series of laminae formed by the fibres from each posterior nerve root, each lamina being displaced medially by that from the next more cranial root. The fibres from the caudal roots form the FG, and those from the more cranial roots the FC. This concept dates from the last century, being mainly based on the study of fibres degenerating after lesions of single posterior roots in man, and on similar studies after experimental lesions in animals. This evidence is well reviewed by Barker (1899). In this century, the most important papers on man are those of Winkler (1918) and Foerster (1936). These papers have resulted in two patterns of the segmental location of the long ascending fibres being commonly accepted. In both, the pattern is the same for the gracile and cuneate fasciculi. These patterns are usually shown at a high cervical segment as in fig. 1A and B.

In the pattern according to Winkler, fig. 1A, the laminae of fibres from each segment are arranged in an oblique plane, radiating from the median septum in an anteromedial posterolateral direction. None of the fibres has any contact with the central grey matter. In the pattern according to Foerster, fig. 1B, each lamina lies roughly parallel to the median septum, extending from the grey matter anteriorly to the periphery of the cord posteriorly.

Another very important paper is that of Walker and Weaver (1942) on the macaque. This is a systematic study of the somatotopic organization of the ascending fibres. Their concept of the location of the fibres from different segments at different cord levels is shown in fig. 2.

In all three patterns the laminae of the fibres from all the posterior roots are shown as having a constant relationship with each other, forming a continuous

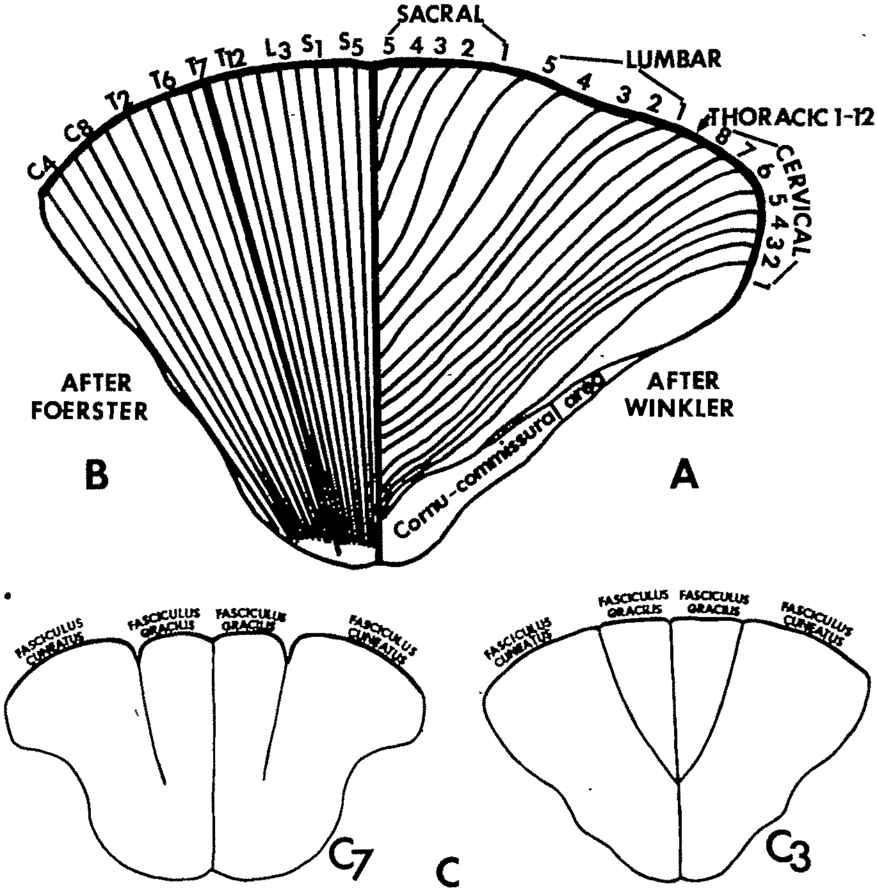

FIG. 1A, B. Segmental organization of the long ascending fibres of the posterior columns in man. A, according to Winkler (1918). Simplified copy of his fig. 110. B, according to Foerster (1936). Copy of his fig. 67. C, diagrams showing customary method of indicating separation of FG and FC by the paramedian septum in the third and seventh cervical segments of the human spinal cord.

series, there being no distinction between the pattern of those in the FG from those in the FC. One or other of these patterns is included in current textbooks of neuroanatomy or reviews concerned with the posterior columns: for example, Crosby *et al.*, (1962) give the pattern according to Winkler, Warwick and Williams (1980) that according to Foerster, and Norton (1969) that of Walker and Weaver.

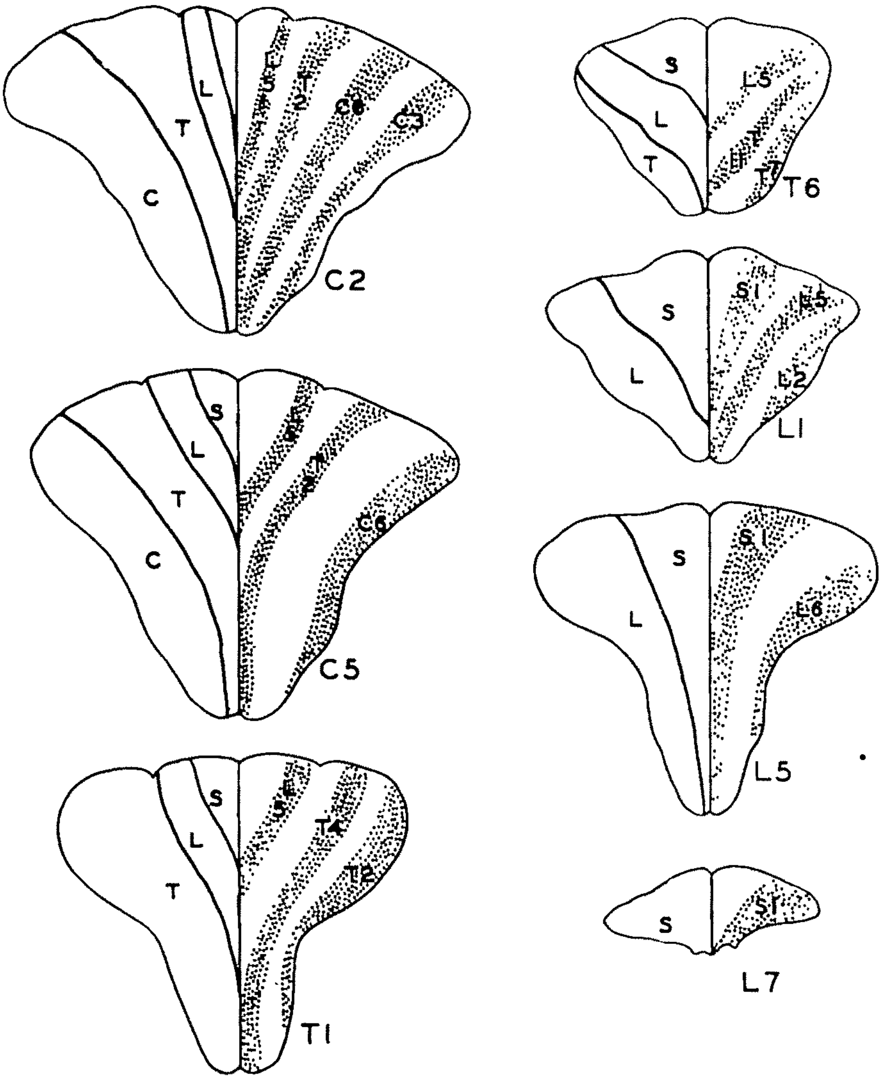

FIG. 2 Reproduction of fig. 4 from Walker and Weaver (1942). (By courtesy of Dr A. E. Walker and the Editor, *Journal of Comparative Neurology*.) Diagrams show somatotopic organization of the ascending fibres in the posterior columns of *Macaca mulatta*, based on degeneration after posterior root section.

In addition to the diagrams showing the lamination patterns, most textbooks also include diagrams such as those in fig. 1c. These show a septum, the paramedian septum, lying between the FG and the FC. The septum is shown as separating the fasciculi completely in C3, but only partially, in their most posterior part, in C7. How the location of this septum fits in with the pattern of lamination shown is never discussed.

Little work has been done on the topography of the posterior columns at different segmental levels of the human cord, and it is on the basis of one or other of these diagrams that interpretations are made regarding which fibres are likely to have been destroyed in lesions of the posterior columns or which fibres are likely to be activated when therapeutic electrical stimulation is undertaken.

Aspects of each pattern are applicable to the relationships of the ascending fibres, but at different levels of the cord. Evidence is presented in this paper to show that the concept of a basic pattern applicable to all segments is an oversimplification. Our investigations were made on man, and based on normal human cords and on cords in which there is degeneration of nerve fibres in the posterior columns due to lesions of the posterior nerve roots or of the columns themselves.

The main points we will consider are the following: (1) the topographical arrangement of the long ascending fibres in different segments of the cord; (2) that the FG and the FC are almost entirely separate, although contiguous, entities; (3) that the shape of the FG in transverse sections is different in, and characteristic of, each of the upper thoracic and cervical segments; (4) that the pattern of segmental lamination in the FG is not identical in all segments; (5) that, although there is a degree of segmental lamination in the FG, there is very extensive overlap of fibres; (6) that there is probably no overlap of fibres from the FC to the FG; (7) that the pattern of lamination and the degree of overlap of fibres in the FC resembles that in the caudal part of the FG, which is different from that in the cranial part of the FG; (8) that the most medial fibres of the FC lying along the lateral border of the FG are in proximity with fibres, in that fasciculus, from many different segments.

MATERIAL AND METHODS

Material

Seventy-eight cases have been studied. These consist of 15 normal spinal cords, 33 cords with lesions of the posterior roots, 8 with lesions of both posterior roots and spinal cord, 14 cords with total (3) or partial (11) lesions of the cord itself, and 8 cases with degeneration in the posterior columns due to neurological disease.

The majority of the cords come from patients who have had anterolateral cordotomies for the relief of intractable pain due to malignant disease. In 41 of these cords there was degeneration in the posterior nerve roots due to involvement in tumour, or to chemical rhizotomy, or to the surgical division of the roots, purposely made in the course of the cordotomy operation, or to a combination of two or all of these causes.

Methods

Blocks from all or the majority of segments were prepared in all cases. Celloidin embedding was mainly used and sections were prepared by a wide range of neurohistological methods, including Weigert Pal, Loyez, Häggqvist, Marchi, Gros-Bielschowsky, Marsland, Glees and Erikson (original method and modifications) and Nauta. The majority of the blocks were cut in the transverse plane.

A number of the cases belong to a large series that are also being studied in relation to other aspects of the topographical anatomy of individual segments of the cord. For all aspects of this work precise identification of the segments has been made, to ensure that observations in different cords are made on the same segment. The level of entry of the most cranial posterior nerve roots has been taken as the upper border of each segment.

RESULTS

Shape of FG and FC in Transverse Section

In the majority of histological sections the distinction between the FG and the FC is not usually evident. It becomes clearer in the upper cervical cord, especially in the third cervical segment, but with special staining methods the fasciculi can be distinguished in some other segments. The two fasciculi can be much more easily recognized when one or other of them is degenerated. From a study of such cases, the shape of each fasciculus can be established, in transverse section, in different segments of the spinal cord.

The first 2 cases show that the shape of the two fasciculi, in transverse section, is different in all sections of the upper thoracic and cervical cord, this pattern being sufficiently different to be characteristic of each segment. These observations can be seen to be confirmed in all the other cases illustrated here.

Case 1 (fig. 3). Collapse of vertebrae has caused almost total degeneration in the posterior columns in the seventh and eighth thoracic segments, the most medial part being very slightly less affected (T8A). Almost the entire FG is therefore degenerated on both sides. There is also some degeneration of the sixth thoracic roots. Degeneration is shown by black staining. In T6 there is ascending degeneration throughout the columns; some of the entering sixth thoracic roots are not degenerating, and appear as paler, lateral areas. As the degeneration is traced cranially, T4 and T2, the main mass can be seen to be broad in the posterior part of the cord, narrowing anteriorly, with a foot extending along the posterior aspect of the central grey matter, its shape resembling that of a Greek vase. In these segments, the degenerating fibres from T6 can be seen to be lying on the periphery of the normal FC and on the lateral aspect of the main mass of degeneration. In the lower cervical segments (C7) the vase is narrower throughout, but with an undulating outline, being somewhat broader on the periphery, in its medial part, and in its foot. In the midcervical segments (C5) the shape is like a pipette, the broad posterior part curving anteromedially to form a much narrower anterior part. In the fourth and third cervical segments (C3) the anterior part becomes extremely narrow, very few, if any, fibres reaching to the grey matter. The anterior part of the FC here lies along the median septum, anterior to the FG. In the upper two cervical segments (C1) the two

FG form a triangle, broad posteriorly, narrow anteriorly, again reaching to the grey matter. In the cervical segments the degenerating fibres from the T6 roots are few in number. They lie along the lateral border of the degenerating FG, scattered in a narrow zone in the most medial part of the FC.

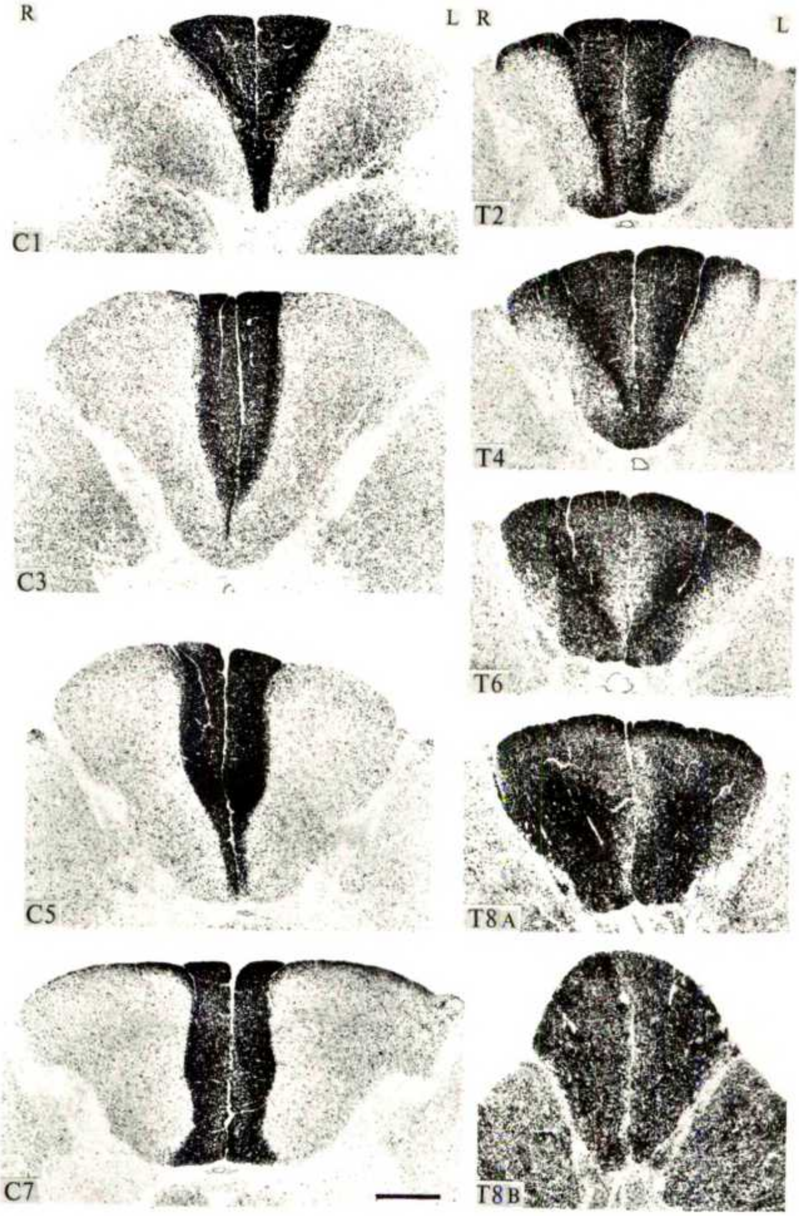

FIG. 3. *Case 1*. Degeneration of both FG following transverse lesion of T7 and 8. *See text* for details. Black staining indicates degeneration. (Marchi preparations. Bar = 1 mm.)

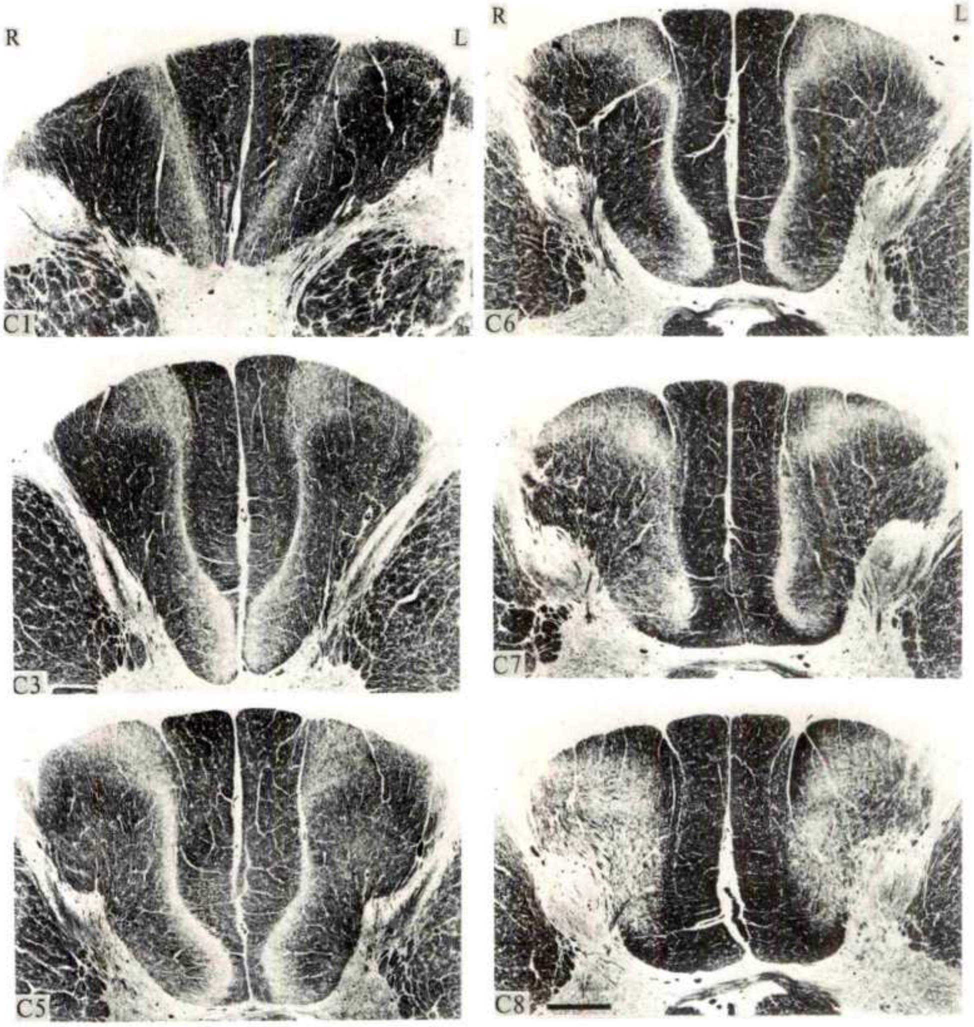

FIG. 4. *Case 2.* Degeneration due to loss of fibres from C8 and T1 posterior roots bilaterally. Pallor indicates degeneration. (Loyez preparations. Bar = 1 mm.)

Case 2 (fig. 4). In this case there is degeneration of both eighth cervical and first thoracic posterior nerve roots (C8). Pallor indicates degeneration. The degenerated laminae can be seen to have migrated medially by C7, lying along the lateral aspect of the normal FG and so outlining them. The shape of the FG in this and the rest of the cranial segments shown here in C6, C5, C3 and C1 can be seen to be essentially the same as that described in Case 1.

It should be noted in both these cases how the size of the FC increases markedly in the lower and midcervical segments, and how this alters the relationship of the two fasciculi. From the sixth to the third cervical segments the anterior part of the two

FC come closer together until they lie along the median septum in the third and fourth cervical segments. As very few, if any, fibres of the FG are in this location in these segments, the FC therefore lies anterior to, as well as lateral to, the FG.

In the two upper cervical segments the FG again extends anteriorly to be in contact with the central grey matter.

Comment on Cases 1 and 2. These two cases illustrate the constancy of the shape of the FG in transverse sections of different segments of the upper thoracic and cervical cord, the shape being different in, and characteristic of, each segment. The shape of the FC is obviously also different in each segment; its medial border is the same as the lateral border of the FG, its lateral border is determined by the size and shape of the posterior horn. The cases also show the clear distinction which exists between the FG and FC in upper thoracic and cervical segments.

Location of Fibres of Different Segmental Origin Within the FG

Case 3 (figs. 5 and 6). There is degeneration of the third and fourth sacral and the first lumbar roots on both sides, and the second lumbar root on the left. Black staining indicates degeneration.

In S3 the degenerating fibres fill most of the FG, except the most anterior and medial parts. In S2 the fibres have shifted medially, displaced by the normal fibres of S2. The lamina of the degenerating S3 and S4 fibres is in the form of a broad band roughly C-shaped lying along the periphery and continuing anteriorly lying lateral and parallel to the median septum, being separated from it by normal fibres, and curving laterally in the anterior part of the column. In the peripheral zone there is a suggestion of two groups of fibres, one lying external to the other. This is the only region where there is possibly evidence that two roots were degenerating; elsewhere there is complete overlap. The lateral curving of the fibres anteriorly is characteristic of the pattern of sacral and lumbar fibres and is due to the presence of the normal fibres of the cornu-commissural tract, which is especially large in the caudal part of the cord. In T10 the degenerating fibres lie more medially. They are most numerous in a triangular area in the posterior part of the columns and within a narrow band along the lateral aspect of the median septum. Degenerating fibres are also scattered more diffusely, lateral to the main concentration. In this segment the degenerating fibres from the lumbar roots are also present. The lamina of degeneration is larger on the left as it is derived from two roots on this side, but there is no differentiation between the fibres coming from the first and those from the second lumbar roots. The laminae are C-shaped, but less markedly so than are the laminae from the sacral segments in S2. In T9 the lumbar degeneration lies slightly more medially, and it is more diffuse in its posterior peripheral part. The lamina of the degenerating fibres extends obliquely in an anteromedial posterolateral direction. In T2 the lumbar fibres have moved medially. The entire FG is clearly recognizable here, degenerating fibres being present throughout the fasciculi, though somewhat more numerous in the peripheral and median zones and along the lateral borders. In C7 also the characteristic shape of the FG is recognizable, degenerating fibres being present

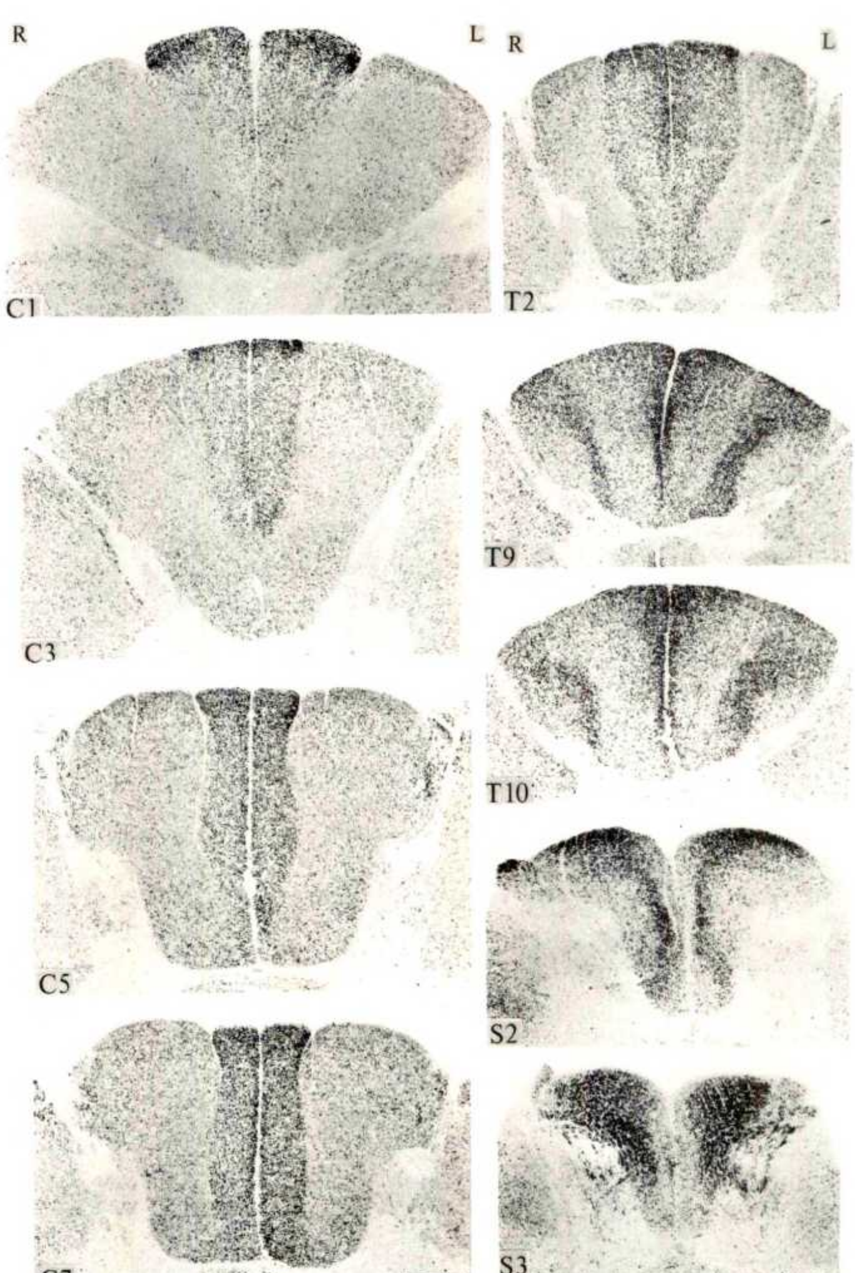

FIG. 5. *Case 3*. Degeneration in fibres from posterior roots of L1, S3 and S4 on right, and L1 and L2, S3 and S4 on left. Black staining indicates degeneration. (Marchi preparations. Bar = 1 mm.)

throughout, including the anterior 'foot' area. In C5, C3 and C1 there is a gradual concentration of fibres posteriorly, but in all the segments degenerating fibres are also scattered throughout the entire fasciculus, which in each segment has the shape described in the previous two cases.

Comment on Case 3. The most important evidence from this case is that fibres from 1 lumbar and 2 sacral nerve roots are present, scattered throughout the entire FG. Although they are more numerous in some areas than others, more sacral fibres lying medially, and more lumbar laterally, in most of the sections, their widespread distribution is clearly very marked.

Lamination in the FG

The next two cases provide evidence regarding the location and relationships of fibres from sacral, lumbar and lower thoracic roots in different segments.

Case 4 (fig. 6A, B; fig. 7). In this case there is extensive loss of lumbar and sacral posterior root fibres. As a result, the normal fibres which enter the FG from intact roots, cranial to the degenerating fibres, stand out, and their location in different segments can be determined. Also, as more roots are degenerating on one side than on the other, a comparison of the fibre pattern on the two sides can be made.

All the sections are myelin preparations, in which pallor indicates degeneration, except S3 and L3 which are Marchi preparations, black staining indicating degeneration. There is degeneration of fibres from all roots from the first lumbar caudally on the left, and from the fourth lumbar on the right. The degeneration is most marked in the roots from L2 to L5 and from S3 on the left, and from L5 to S3 on the right; its extent can be appreciated from the section of L3 in which the degeneration is stained black. In all the other sections, in which pallor indicates degeneration, the almost total loss of fibres from these roots has resulted in a broad lamina on each side, standing out by its extreme pallor. In the caudal sections, L3 to S1, the degenerating laminae have a C-shape conforming to the location of posterior root fibres in these segments, roughly parallel to the medial aspect of the posterior horn. In the upper lumbar and lowest thoracic segments, L2 to T11, the laminae gradually become straighter, lying in anteroposterior bands, roughly parallel to the median septum. The orientation of the laminae alters somewhat in the next few segments, T9, T7, where they lie in a slightly oblique anteromedial posterolateral plane.

The very clear evidence of lamination in the caudal segments is lost in more cranial segments, owing to the increasing overlapping of degenerating laminae medially, with those fibres derived from less affected caudal roots, and owing to the entrance laterally of fibres from the normal more cranial roots. The degeneration of some sacral root fibres on both sides (shown in S1 and S3), has resulted in some reduction of the fibre density in the most medial part of the fasciculi, along the median septum. Nevertheless, the contrast in the appearance in this region with the very degenerated pale laminae lateral to them is most striking up to about L2; more cranially the distinction between them becomes blurred because of overlapping of the medial fibres by the extremely pale laminae.

Normal posterior root fibres from L4 cranially on the right and L1 cranially on the left gradually migrate medially, overlapping the degenerated laminae as seen in T11. By T9 a fairly sharp distinction can be made between the dark staining normal fibres in the lateral half of the fasciculus on each side, and the medial part of the fasciculi, where there is fibre loss. But there is a considerable difference between the appearance of the medial areas on the two sides. On the left a narrow band of normal fibres lies within the anterolateral third of the medial area. On the right many more normal fibres are present within this area; they are most numerous laterally, but extend throughout the area which, on the left side, is occupied by the pale lamina. It can be deduced that these normal fibres on the right come from the upper 4 lumbar roots and possibly also from the lowest 3 thoracic roots. The normal fibres on the left can have come only from the first lumbar and possibly the lowest 3 thoracic roots. The oblique lamination of fibres noted earlier in the lower thoracic cord is also maintained in the more cranial segments. It appears that the lamination is in the anteromedial posterolateral plane, the most anterior lamina being from the lowest thoracic segments and the most posterior from sacral segments. But it must be stressed that the lamination only denotes where the greatest density of fibres from any root is concentrated. The overlap of fibres from different roots is very marked. This is shown in this case by the fact that the palest zone, that is, the zone of maximum loss of lumbar and sacral fibres, is still recognizable in T7 and all segments cranial to it, and that this zone extends anteriorly right up to the central grey matter in all segments where the FG reaches the grey matter.

In all the segments from T5 cranially the oblique lamination of fibres can be recognized, although the intermingling of fibres makes it less obvious in the lower cervical segments. In C7 the anterior part of the lateral margin of the FG cannot be clearly distinguished, as the normal fibres of the FC lie in close proximity to the normal upper lumbar and lower thoracic fibres on the right and the normal lower thoracic fibres on the left. The entire area occupied by the FG can be estimated by reference to the first two cases. In C4 the border between the FG and the FC can be recognized, and the normal fibres in the FG appear to be more densely packed here and to be lying in a more posterior location. The oblique lamination can best be appreciated by comparing the two sides. This applies also to C2, where the FG have a triangular shape, the anterior part being narrower and in contact with the grey matter.

Comment on Cases 4 and 5. These two cases have shown that there is a certain degree of lamination of fibres in the FG. The orientation of the laminae is not the same throughout the caudocranial extent of the fasciculus. In the most caudal segments, the sacral and lower lumbar, the laminae are roughly parallel to the medial border of the posterior horn; in the upper lumbar and lower thoracic segments they are roughly parallel to the median septum; throughout the rest of the cord the lamination is oblique in an anteromedial posterolateral orientation, the obliquity being less marked in the upper two cervical segments. These cases have also shown that the lamination indicates only the major concentration of fibres from

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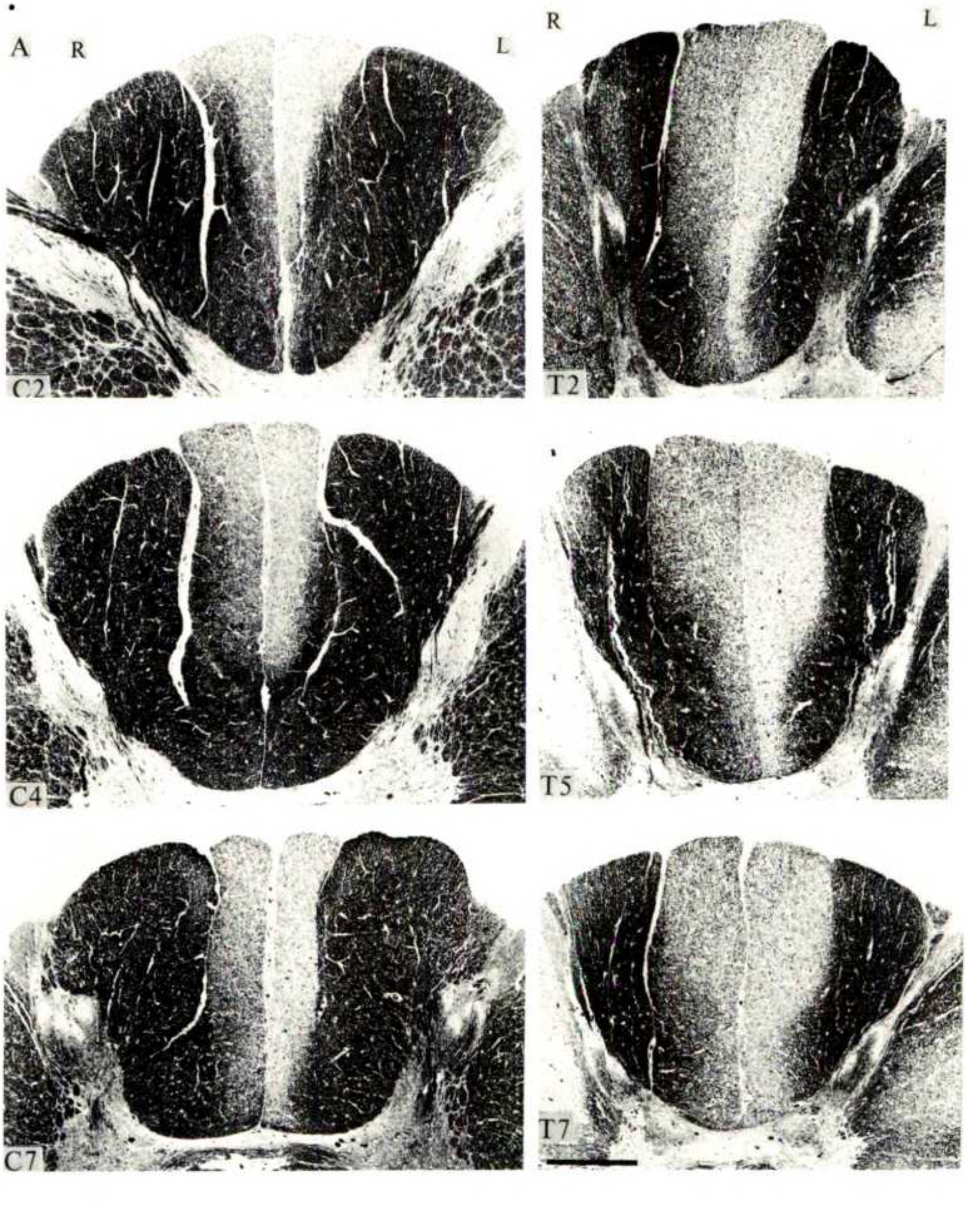
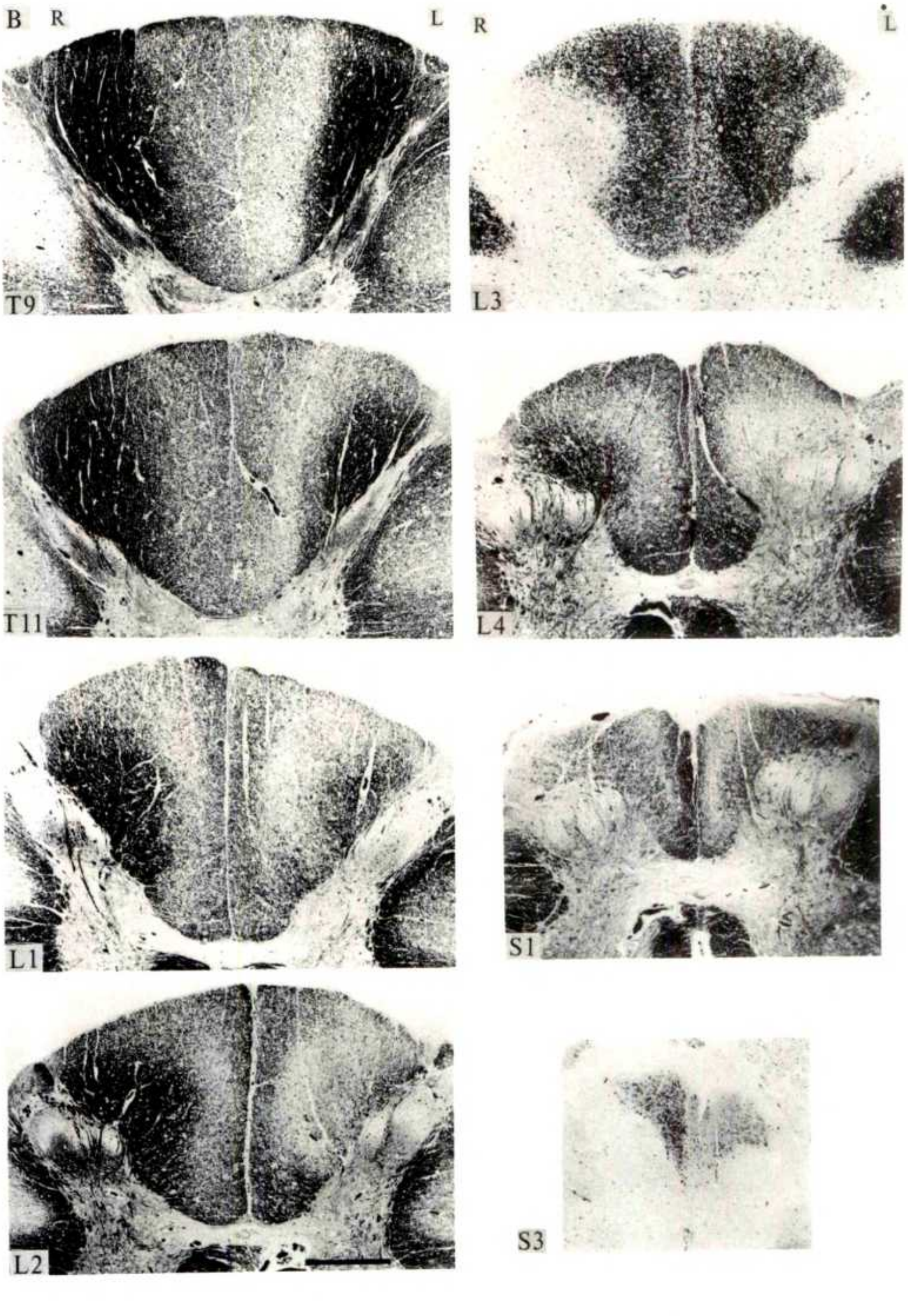


FIG. 6A, B. *Case 4*. Degeneration due to loss of fibres from lumbar and sacral posterior roots. *See text* for details. Pallor indicates degeneration except in L3 and S3, where black staining indicates degeneration (Weigert Pal or Loyez preparations in all sections except L3 and S3 which are Marchi preparations. Bar = 1 mm.)


B
R
L
R
L
T9
L3
T11
L4
L1
S1
L2
S3

different roots. Fibres from all the sacral and lumbar roots are scattered throughout the FG. The fibres from the lower thoracic roots are fewer in number and may not be so diffusely distributed.

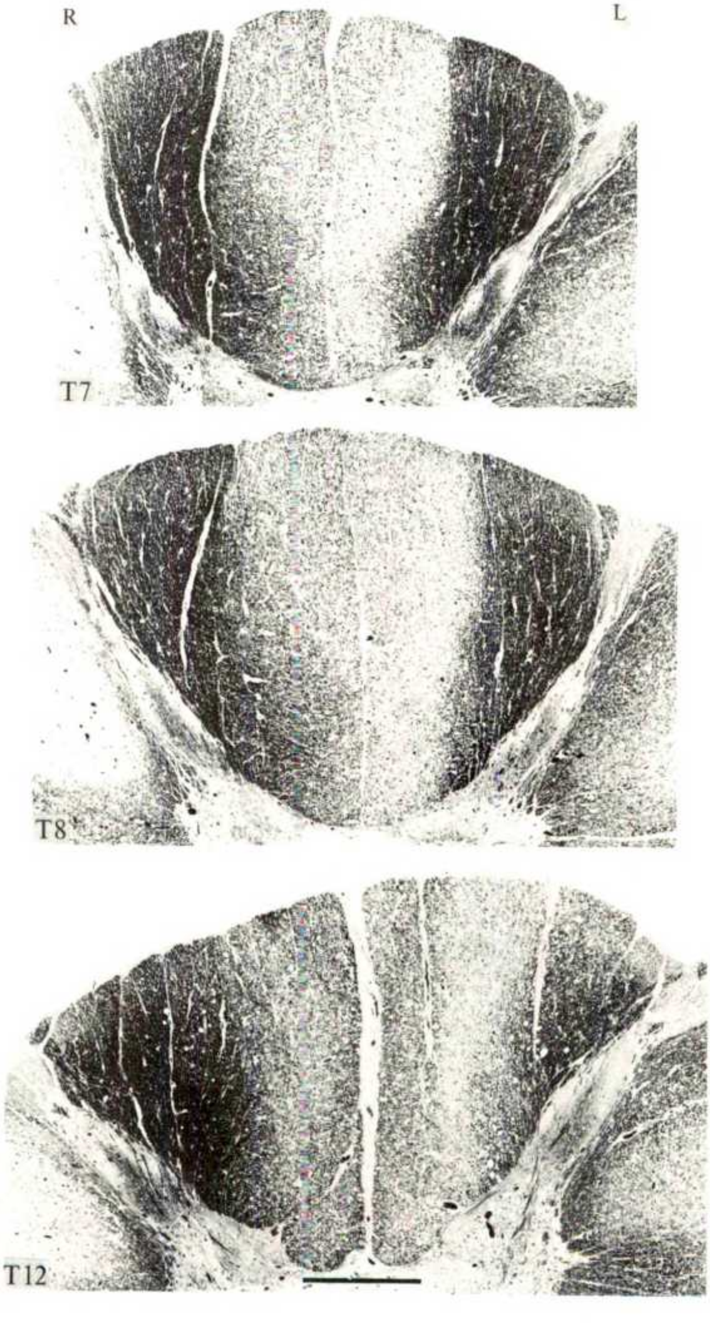


FIG. 7. *Case 4.* Degeneration due to loss of fibres from lumbar and sacral posterior roots showing effect of paramedian septum on fibre pattern. *See text* for details. Pallor indicates degeneration (Loyez preparations. Bar = 1 mm.)

The Paramedian Septum

The next points to be considered are the separation of the FG and the FC by the paramedian septum and the influence of the septum on the fibre pattern in the FG. These points are illustrated from Case 4 (figs. 7 and 8) and from Case 5 (fig. 9). In Case 5, as in Case 4, there is loss of fibres from lumbosacral roots, which is greater in this case on the right side.

The paramedian septum appears in the sixth or seventh thoracic segment and it is present in all more cranial segments. It extends from the periphery of the cord anteriorly for about one half of the depth of the column. The posterior part of the septum is often, but not always, clearly defined by the presence of a blood vessel. This vessel itself, or a major branch of it, frequently diverges laterally away from the septum, either close to the periphery (fig. 9, T3) or more anteriorly (fig. 8, T2). That the paramedian septum acts as a barrier to the medial migration of fibres can be appreciated by comparing the appearance of sections in which it is not present, with that of sections in which it is.

In fig. 7 the obvious medial migration of fibres along the whole anteroposterior extent of the column, seen in T12 and T8, is not seen in T7, nor is it seen in fig. 8, T2. There is, in these two segments, a sharp distinction between the medial and lateral parts of the column, except in the anterior third. In the anterior part of the column in the more cranial segments the appearance suggests that some fibres have migrated medially, anterior to the free edge of the septum.

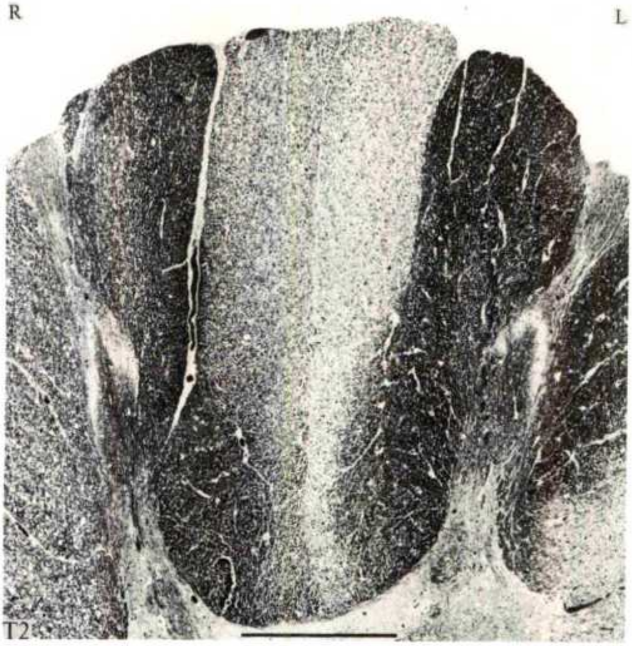


FIG. 8. *Case 4.* Degeneration due to loss of fibres from lumbar and sacral posterior roots showing effect of paramedian septum on fibre pattern. *See text* for details. Pallor indicates degeneration. (Loyez preparation. Bar = 1 mm.)

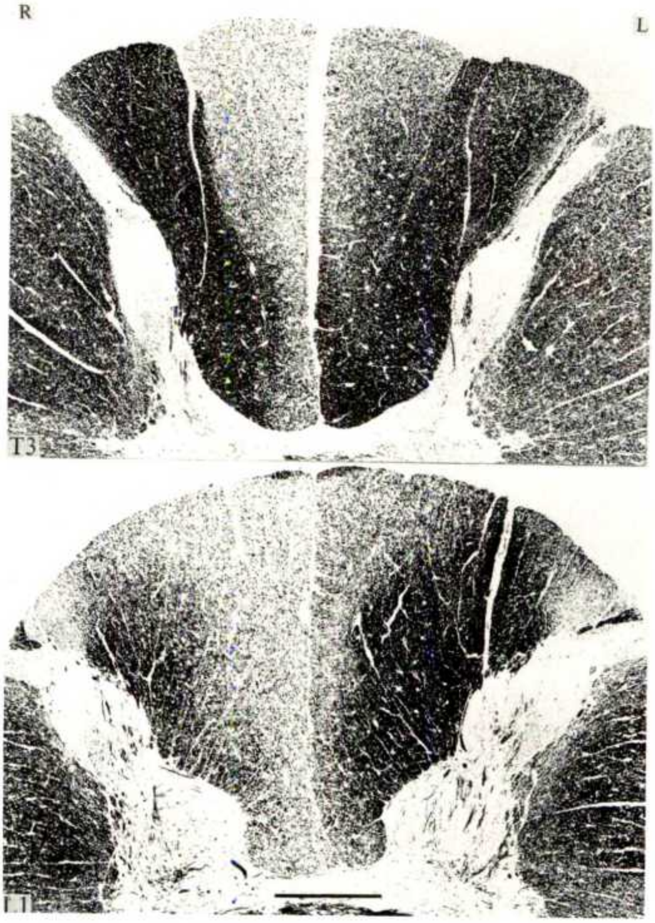


FIG. 9. *Case 5.* Degeneration due to loss of fibres from lumbar and sacral roots showing different appearance in section L1, without paramedian septum, and section T3, with paramedian septum. Pallor indicates degeneration. *See text* for details. (Weigert Pal preparations. Bar = 1 mm.)

The same contrast between segments in which there is no paramedian septum and those segments in which there is a paramedian septum, is seen in fig. 9, in L1 and T3.

In the lowest segment in which the paramedian septum is present the entire posterior column consists of the FG, but the paramedian septum divides it into a medial and a lateral section. The medial section contains the posterior root fibres from all the caudal segments except those from the segment immediately caudal to it, and from the root of that segment itself. These fibres, from the seventh and the eighth segments, lie lateral to the paramedian septum in T7 and migrate medially in the next two segments to lie in the anterolateral part of the FG (fig. 8, T2; fig. 9, T3). All the fibres from the sixth root cranially remain lateral to the septum and they form the FC.

The appearance of the posterior columns from the sixth or seventh thoracic segment to the first thoracic segment does not change greatly from segment to segment. In all these segments, the paramedian septum divides the columns into two parts. In the upper thoracic segments the medial part contains fibres going to the nucleus gracilis and the lateral part fibres destined for the nucleus cuneatus. In the lower of these thoracic segments both the medial part and the lateral part contain fibres going to the nucleus gracilis.

Interpretive Value of Knowledge of Fibre Distribution in Posterior Columns

Case 6 (fig. 10). This case shows degeneration in an unusual location. A cordotomy at T3 accidentally transected the anterior part of both FG where the 'foot' lies along the posterior aspect of the grey matter. The location of the degeneration is shown in the upper cervical segments, in C4 by pallor, in C2 and C1 by black staining.

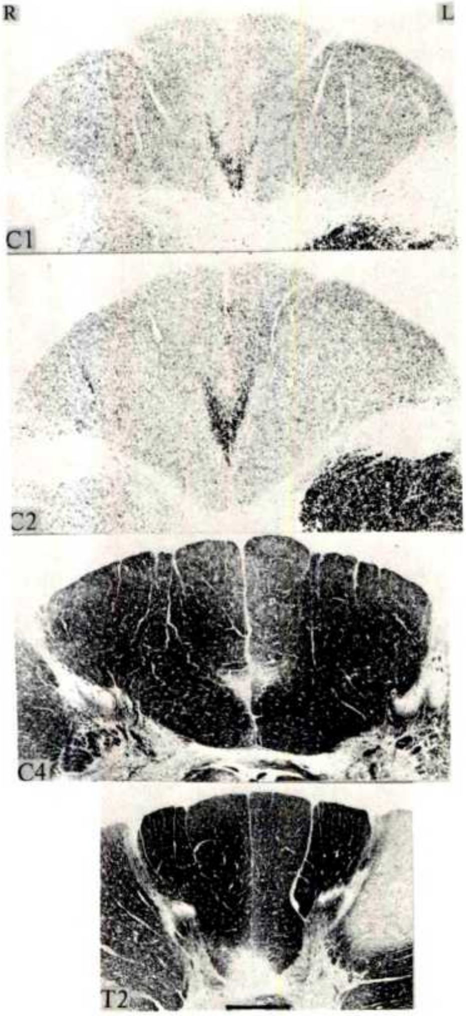


FIG. 10. *Case 6*. Degeneration due to lesion of anterior part of both FG in T3. Degeneration indicated by pallor in T2 and C4, and by black staining in C2 and C1. (Loyez and Marchi preparations. Bar = 1 mm.)

In C4, where the two FG lie posterior, as well as medial, to the FC, the most anterior part of the FG is degenerated and, on the right, slight degeneration extends anteriorly to the grey matter. In C2 and C1 the degeneration is in the form of a V, a narrow band lying in the anterolateral part of each FG.

Comment on Case 6. This case is shown as it demonstrates how a knowledge of the characteristic anatomy of the posterior columns in different segments could help in deducing the probable cause of degeneration in a particular distribution, seen in an upper cervical segment, if no other segments were available for examination.

Location of Fibres within the FC

Case 7. Fig. 11 shows the location of fibres from the posterior roots of the fourth and second thoracic on the left and from the first to third thoracic on the right. It also shows, on the left, the location of fibres from the second cervical root. The degeneration is stained black. The diffuse black staining in the FG is artefact.

On the left side of T2 the degeneration from the fourth thoracic root lies in the most medial part of the FC. Normal fibres separate it from the entering degenerating fibres from the second thoracic root. In C7 the degenerating fibres from T2 lie medially, in the form of a narrow C-shaped lamina, lying parallel and slightly lateral to the degenerating lamina from T4. Normal fibres separate these two laminae. In C5 the fibres from the two roots are completely intermingled, forming a lamina of diffusely scattered fibres lying in the most medial part of the FC, along the medial part of the periphery posteriorly, and the medial part of the grey matter anteriorly. The degenerating fibres appear to be distributed more diffusely, in the same location, in C2.

On the right side of T2 the degeneration from T3 and T2 lies in the lateral part of the FC. In C7 these degenerating fibres, together with those from T1, form a wide reversed C-shaped lamina in the most medial part of the FC. The fibres from the different roots cannot be distinguished. The medial border of the lamina is sharply delineated by intense degeneration, whereas the lateral border is not defined, as scattered degenerating fibres are present among the normal fibres lying lateral to it. A comparison of the two sides allows the conclusion that this lamina of T1, 2 and 3 fibres occupies the same medial areas as the degenerated T2 and T4 fibres, and the interposed normal T3 fibres, on the left side. In C5 the lamina of degeneration on the right clearly defines the FG, its anterior part curving further medially than in C7, and then extending along the posterior aspect of the central grey matter. The degeneration on the periphery is rather diffuse and a slight distinction can be made between the scattered fibres on the periphery and a deeper more concentrated group, lying parallel to the periphery. This group is in continuity with the main mass of the lamina, lying along the paramedian septum. In C2 the lamina of degeneration is in the form of a reversed L lying slightly deep to the entire length of the periphery of the FC and along its medial border. The most intense degeneration is in the centre of the lamina, scattered degeneration lying on either side of it.

On the left, in C2, the degenerating fibres from the C2 root are seen in the FC, slightly cranial to their entrance into the cord. They lie in the most lateral part of the FC, in a triangular area, deep to the periphery. The base of the triangle extends along approximately the second and third fifths of the anterolateral border of the FC.

Case 8 (fig. 12). The degenerating fibres in this case come from the roots of T2 on the left and C1 on the right. As the pattern of T2 degeneration has been described in the previous case it will not be discussed in detail; certain features only will be noted.

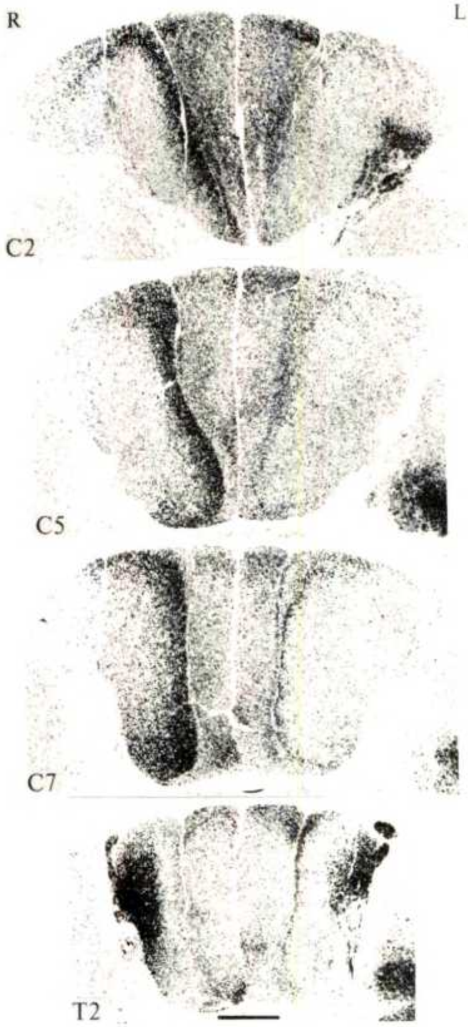


FIG. 11. *Case 7.* Degeneration from posterior roots of T2, T4 and C2 on left and from T1-3 on right. Black staining indicates degeneration. Black staining in FG is artefact. (Marchi preparations. Bar = 1 mm.)

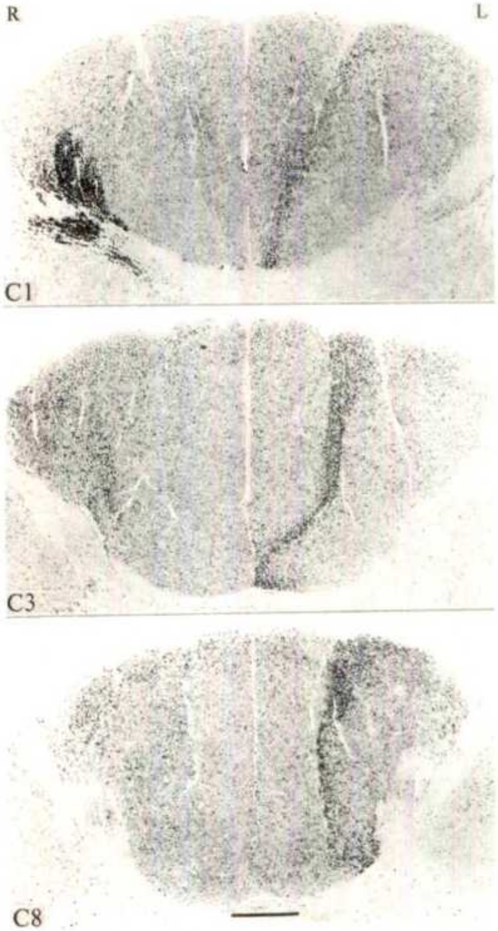


FIG. 12. *Case 8.* Degeneration from posterior roots of T2 on left and C1 on right. Black staining indicates degeneration. (Marchi preparations. Bar = 1 mm.)

In the section of C8 the lamina of degeneration consists of rather diffuse scattered fibres especially at the two ends of the lamina. In C3 the lamina is more compact and it shows very clearly the shape of the FG, and how the fibres lie along the lateral aspect of the paramedian septum and along the posterior aspect of the medial part of the central grey matter. The degeneration in C1 is scattered along the lateral aspect of the paramedian septum, resembling that from T4 and T2 in Case 7. This case confirms the marked overlapping of fibres from different roots in the medial part of the FC.

On the right side the degenerating fibres from the C1 root lie in a similar location to those of C2 shown in Case 7.

Case 9 (fig. 13). The degenerating fibres on the right side come from the roots of C8 and T1 and to a lesser extent T2. On the left, C2 is degenerating. The broad lamina of degeneration on the right resembles that seen on the right side in Case 7; although it is derived from several roots it appears as a single lamina until C6, where two groups of fibres can be identified in the posterior part. The separation of these two groups becomes even more marked in C3 and C2. In the most cranial section, at the lowest level of the medulla (M), the separation into two parts is very clear, the more medial group lying along the medial border of the FC, the more lateral group roughly parallel to it, and its posterolateral part lying deep to the surface. The area between these two laminae contains fewer degenerating fibres.

On the left side the degenerating C2 fibres in the FC have the same location as those of C2 in Case 7, and C1 in Case 8.

Comment on Cases 7, 8 and 9. Aspects of the pattern of degeneration in these 3 cases can be seen also in Case 2, fig. 4. In all 4 cases the degeneration from the affected roots is limited to the FC. The clear outlining of the FG by the degeneration in the FC is one of the notable features of all these cases. This is so, even although the paramedian septum is present only in the posterior part of the cord in the lower cervical and upper thoraccc segments.

Case 7, in which there is degeneration of T4, provides evidence that this root runs in the FC, not in the FG, as is sometimes stated (Glees and Soler, 1953; Soler, 1958).

With respect to T5 and T6 our evidence is less good, but what there is suggests that these roots also run in the FC, and that they lie close to the paramedian septum in the upper cervical cord. This observation is confirmed in other cases that we have studied. We do not have cases showing the pattern of the location of the fibres from C3 to C7, but the evidence we have justifies deductions about all the fibres in the FC, at least as far caudal as T4.

If the right side of C2 in Case 7 (fig. 11) and Case 9 (fig. 13) are each superimposed on the left side of the same case, it can be deduced that in this segment the laminae from successively higher roots lie in a series of inverted Ls, each one deeper below the periphery, and more lateral, than its preceding lamina. A comparable relationship will exist also in the lower segments. The overlapping of fibres from different roots is marked, especially in relation to the small contingents of fibres from the second to the sixth thoracic roots, which become overlapped by the large number of fibres from the first thoracic and the eighth cervical roots.

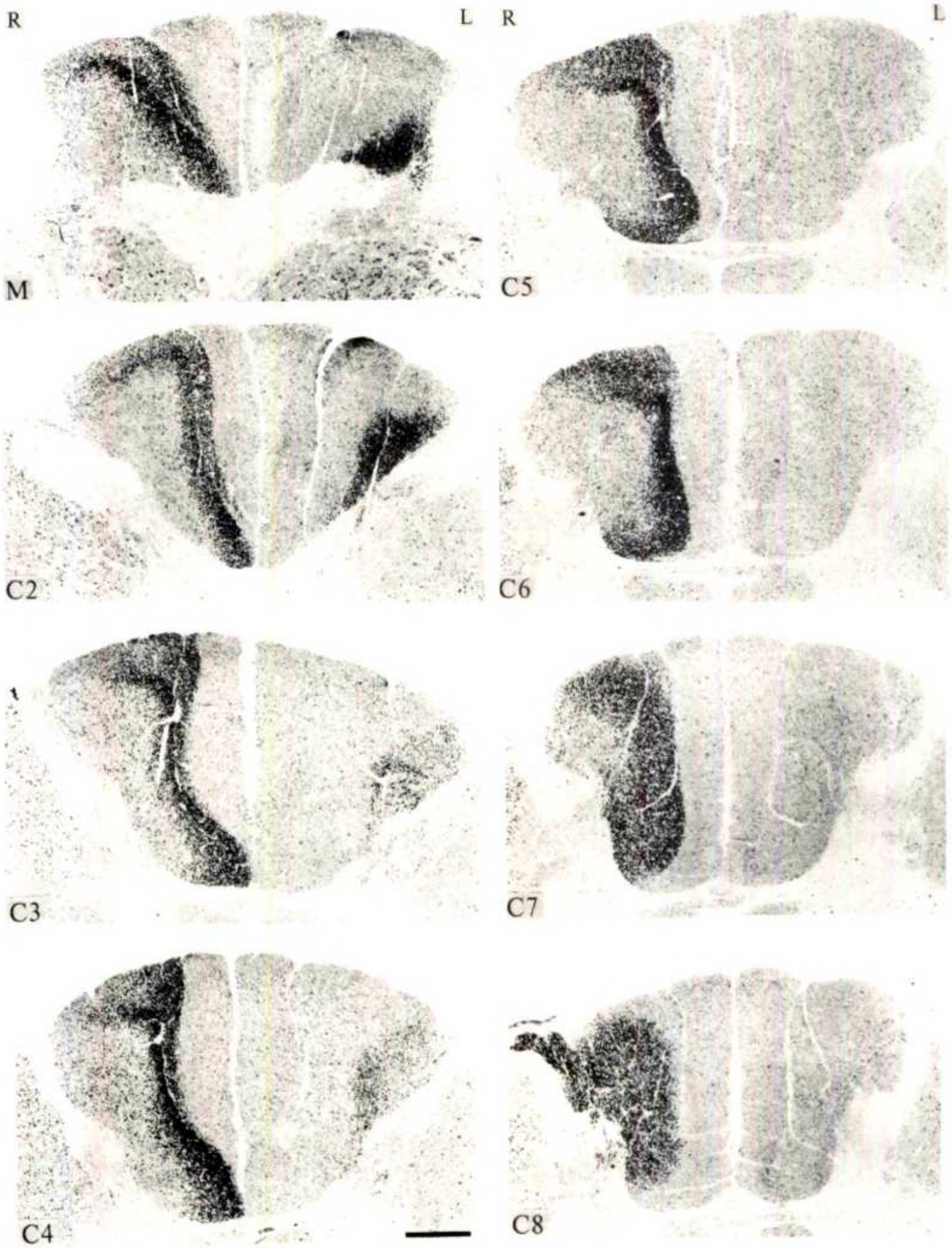


FIG. 13. *Case 9*. Degeneration from posterior roots of C8, T1 and T2 on the right, and C2 on the left shown in sections from cervical cord and medulla (M). Black staining indicates degeneration. (Marchi preparations. Bar = 1 mm.)

The pattern of lamination of the fibres in the FC is similar to that of the FG in its caudal segments, but it is different from the pattern of lamination of the FG in the cranial segments. Further, the intermingling of fibres in the FG is much more extensive than that in the FC. A diagram of a basic pattern showing the relationship of the fibres from the roots of all segments of the cord cannot therefore be drawn.

Summary

Fig. 14 summarizes some of our observations. It shows the seventh cervical segments in 7, and the eighth cervical in 1, of the cases described here. In all the photographs black staining indicates degeneration. The following features of the FG and FC are shown. (1) The clear separation of the FG and the FC. (2) The constant shape of the FG and the FC at this level. (3) The widespread distribution of fibres from different segments in the FG. (4) The pattern of segmental lamination in the FG in oblique anteromedial posterolateral planes, at this level. (5) The extensive intermingling of fibres from adjoining segments in the FC. (6) The pattern of segmental lamination of the FC in anteroposterior planes. (7) The juxtaposition of the most medial of the fibres of the FC with fibres from many caudal segments in the FG.

DISCUSSION

We have presented photographs of sections showing the location of the long ascending fibres from posterior nerve roots in different segments. These show that the fibre pattern is different in every segment of the cord and it therefore cannot be simplified and generalized into a single diagram.

In comparing our conclusions with those of previous workers, Winkler (1918) based his observations on the location of degeneration after posterior root sections in the monkey and the dog, on cases of tabes dorsalis in man, and on Flechsig's studies on myelination. He considered that, due to the presence of the intrinsic fibres of the cornu-commissural tract, the fibres of the posterior column do not come into any contact with the central grey matter, or with the posterior horns. This view was based on his conception of a large cornu-commissural tract extending throughout the length of the spinal cord and along the whole extent of the posterior horn. The pattern of the degenerated and normal fibres observed by Winkler suggested to him a lamination extending from the median septum posterolaterally to the periphery, like the pattern he had observed in the dog.

It has been shown here that in the third cervical segment (*see* fig. 1c) the paramedian septum forms the medial border of the FC, lying roughly parallel to the medial border of the posterior horn. This might suggest that the laminae of fibres in all segments would form a series lying parallel to these borders of the FC, extending from the median septum anteromedially, to the periphery of the cord posterolaterally. Our observations show that this is not so.

An important observation made by Winkler and which we have confirmed, was

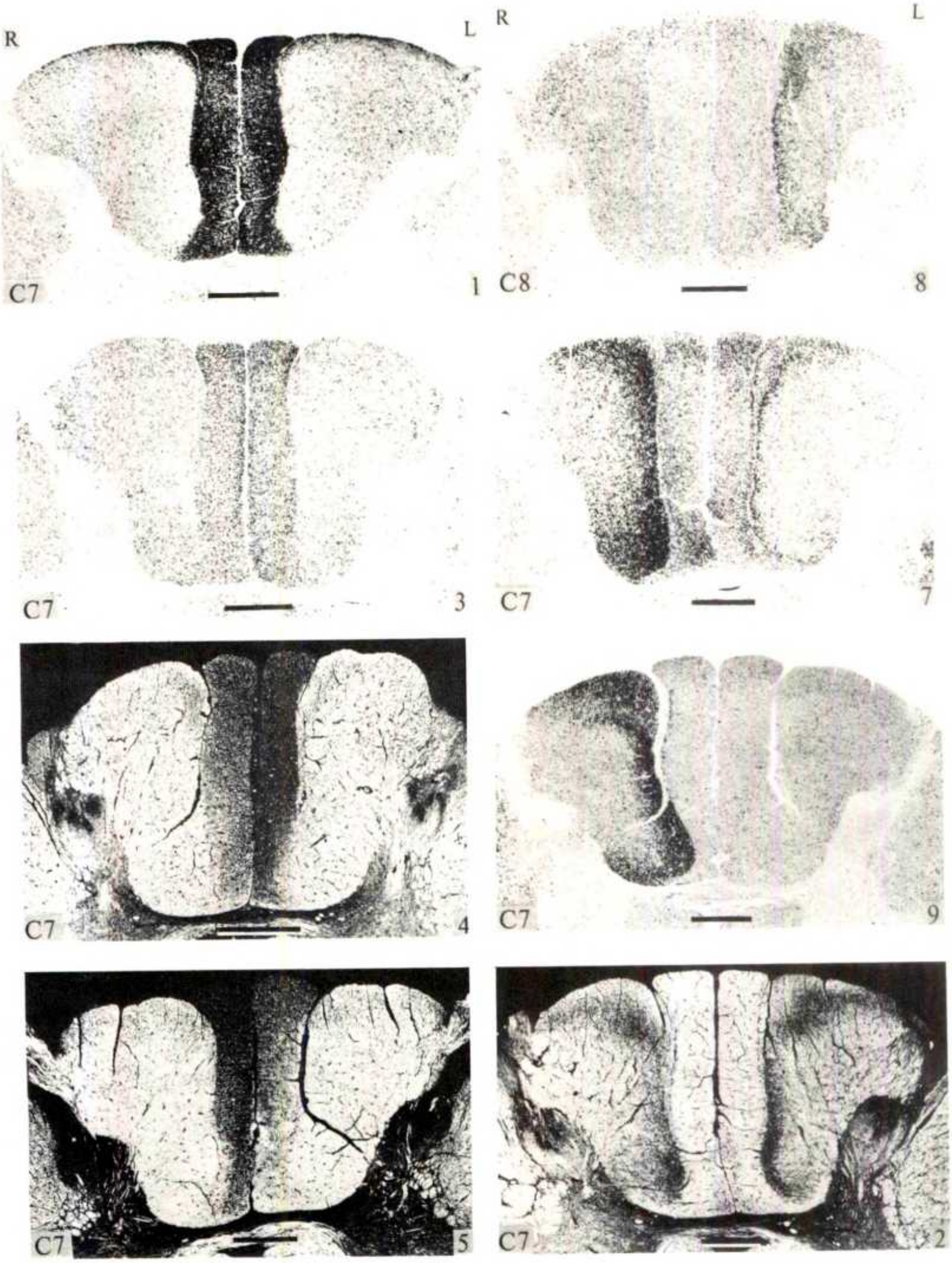


FIG. 14. Sections from same segmental level of 8 cases described in text. Case numbers given on right of prints. In all cases black staining indicates degeneration. *See text* for details. (Marchi preparations and negative prints of myelin preparations. Bar = 1 mm.)

that there is a marked difference in the size of the roots from the cervical and lumbosacral enlargements and those from the thoracic segments. He found that in the monkey it was necessary to cut two or three thoracic roots in order to demonstrate a lamina of degeneration.

On the basis of his observations Winkler drew a general plan of the lamination of the posterior root fibres from every segment of the human cord, from the fifth sacral to the first cervical shown (in a simplified form) in fig. 1A. However, the material that he used did not show details of fibre patterns within the two fasciculi, nor any differences between the fasciculi, nor did he appear to have any material showing degeneration of the ascending fibres from individual roots. Further, several levels of the cord do not seem to have been examined. Generalizations of the relationship of fibres from all the posterior roots cannot be made on such limited material.

With regard to his statement that the cornu-commissural fibres separate the fibres of the posterior column from the central grey matter and posterior horns at all levels we have found that the cornu-commissural tract is large only in the lower lumbosacral segments. Here it causes a lateral deflection of the ascending fibres as they migrate medially, but within one or two segments the ascending fibres intermingle with the cornu-commissural fibres and reach the median septum. The cornu-commissural fibres do not present any barrier to the ascending fibres at more cranial levels of the cord.

In 2 of Foerster's (1936) 5 cases there was extensive bilateral degeneration of lumbar and sacral roots, and in 1 of them the lower thoracic roots were also involved. In the other 3 cases there was degeneration of one or more posterior nerve roots. Foerster stressed that the two FG extended forward to the commissure in all the sections except the second cervical. We note that the shape of the degenerated FG in those segments that he described is the same as that which we have reported here.

Foerster's last case is of particular importance as it shows the relationship of several laminae to each other. This case may be unique: the posterior roots from the second thoracic to the seventh cervical, and the fifth and fourth cervical were resected. The sixth root was left intact. In his diagram of the second cervical segment five laminae are shown, those derived from degenerated roots alternating with those from normal roots. The most medial lamina represents all the fibres from the fifth sacral to the third thoracic. This lamina lies along the median septum, but does not extend anteriorly to reach the central grey matter. The next lamina, from the second thoracic to the seventh cervical has a curved outline, parallel to the medial lamina; it extends from the paramedian septum to the periphery, posterolaterally. It does not reach the central grey matter. These two laminae, comprising all the fibres from the fifth sacral to the seventh cervical roots, occupy about one half of the posterior column. The next two laminae, one from the fifth and sixth cervical roots, the other from the third and fourth, both extend from the central grey matter to the periphery, posterolaterally. They have a curved outline, roughly parallel to the border of the posterior horn. The most lateral lamina, from the second and third cervical roots, lies along the border of the posterior horn, not extending as far anteriorly as the central grey matter.

Our observations are in agreement, on the whole, with those shown by Foerster in these cases, except for his view of the relationship of the majority of the fibres to the median septum, rather than to the central grey matter, in the second cervical segment. It is unfortunate that in the diagram of the lamination pattern which Foerster produced for the organization of the laminae in the posterior columns in the upper cervical cord, shown here in fig. 1B, he has not incorporated his own evidence. In this diagram he has shown the laminae radiating out like the ribs of a half-open fan, all the laminae having the same width and the same anteroposterior length. The most medial are parallel to the median septum, the others being angled obliquely away from this plane, the obliquity increasing in the more lateral laminae. All the laminae are shown to have the same anterior extent as the central grey matter. The column is shown to have two equal halves. The medial half is shown to be composed of fibres from the fifth sacral to the seventh thoracic roots and the lateral half from the sixth thoracic to the second cervical roots. It must be noted that Foerster, as well as Winkler, produced his pattern for the fibres from all the posterior roots on evidence of only a few roots. It may be that Foerster intended this diagram to indicate only the general principle that there is a continuous series of laminae of fibres, their mediolateral relationship representing their caudocranial origin. However, the diagram is generally taken to indicate the actual location of fibres from different roots within the posterior columns, and therefore to serve as a guide to the interpretation of histological sections from different segments.

The third pattern of the lamination of fibres is that of Walker and Weaver (1942). Their diagram is based on much more evidence than those of Winkler and Foerster and shows the location of fibres from different segments at various levels of the cord. Although it refers to the monkey it is closer to our concept of the location of the fibres than either of the other patterns.

There are certain differences in the pattern of fibres given in Walker and Weaver's fig. 4 (our fig. 2) from our concept of the pattern in man, which may be a species difference. Laminae of fibres in the FG are shown to extend to the central grey matter only in the first part of their course in the fasciculus, so that by T6, for example, the lumbar and sacral roots are present only in the posterior part of the fasciculus. In the FC also they shift posteromedially. We found that the FG extends to the anterior grey matter except in the third cervical segment. The FC appears to be much larger in comparison with the FG in man than in the monkey, and the large posterior roots, subserving the upper limb, form elongated laminae each of which curves in the form of a C. Another difference is that the laminae in the monkey appear to be in a continuous series, no division into two fasciculi being indicated. Marked overlap of the fibres from adjacent roots is noted by Walker and Weaver: '. . . while there is a certain segmental arrangement of the fibers of the posterior column there are no individual compartments for each posterior root or spinal segment.' But there is no mention whether this overlapping does or does not occur between fibres of the FG and those of the FC. There is also no mention of a paramedian septum. The clear separation of the FG and FC is one of the features in man that we have stressed, very few, if any, fibres from the laminae in the FC overlapping those in the FG.

The paramedian septum plays an important part in this separation, as we have shown here. It is, however, only a partial septum in most of the segments, extending a short distance into the cord. Nevertheless, the distinction between the two fasciculi is clear cut, as we have shown in cases of degeneration in the FC. It is our opinion that other factors play a part in creating the effect of a barrier between the fasciculi. We are at present studying this aspect of the anatomy in greater detail.

CONCLUSIONS

Our concept of the topographical anatomy of the posterior columns is now summarized. The evidence is that the organization is not identical in the FG and the FC and that these fasciculi must be considered as separate anatomical entities. The pattern of lamination is not the same nor is it the same at all segmental levels of each fasciculus. In the FG, the first fibres to enter are the numerous fibres from the lower limbs, arriving in the sacral and lumbar roots. The main part of this fasciculus is therefore formed before the less numerous thoracic fibres enter. By the midthoracic cord, the FG has already had a considerable course, which offers the possibility of changing relationships among the component fibres. In the FC the first fibres to enter are the relatively few fibres of the upper thoracic roots. The more numerous fibres from the upper limb, which include those from the first thoracic root, come in later. The main part of the FC is therefore formed only in the nine most cranial segments of the cord. Its course is much shorter than that of the FG and so it is likely that the relationships of the entering fibres remain more constant in their course than those in the FG.

The mechanical factors affecting the location of the fibres within the FG are not only the median and the paramedian septa but also the pressure from the large FC. The mechanical factor determining the location of the fibres within the FC is the barrier of the paramedian septum. This, however, may be too mechanical a view of the topography and there may be many other reasons for the changing pattern of lamination.

Whitsel *et al.* (1970) described a resorting of fibres in the FG during their course in the squirrel monkey. This study was based on degeneration studies and on microelectrode recordings. They found that the organization of the fibres was dermatomal in the lumbar cord, and topographical in the cervical cord. It may be that a similar rearrangement of fibres also occurs in the human cord.

A detailed study of the shape of the FG in different segments has not previously been made in man, as far as we know, but illustrations showing ascending degeneration in one or two segments cranial to lesions of the FG included in some earlier papers show the same shape of the FG in these segments as we have reported here

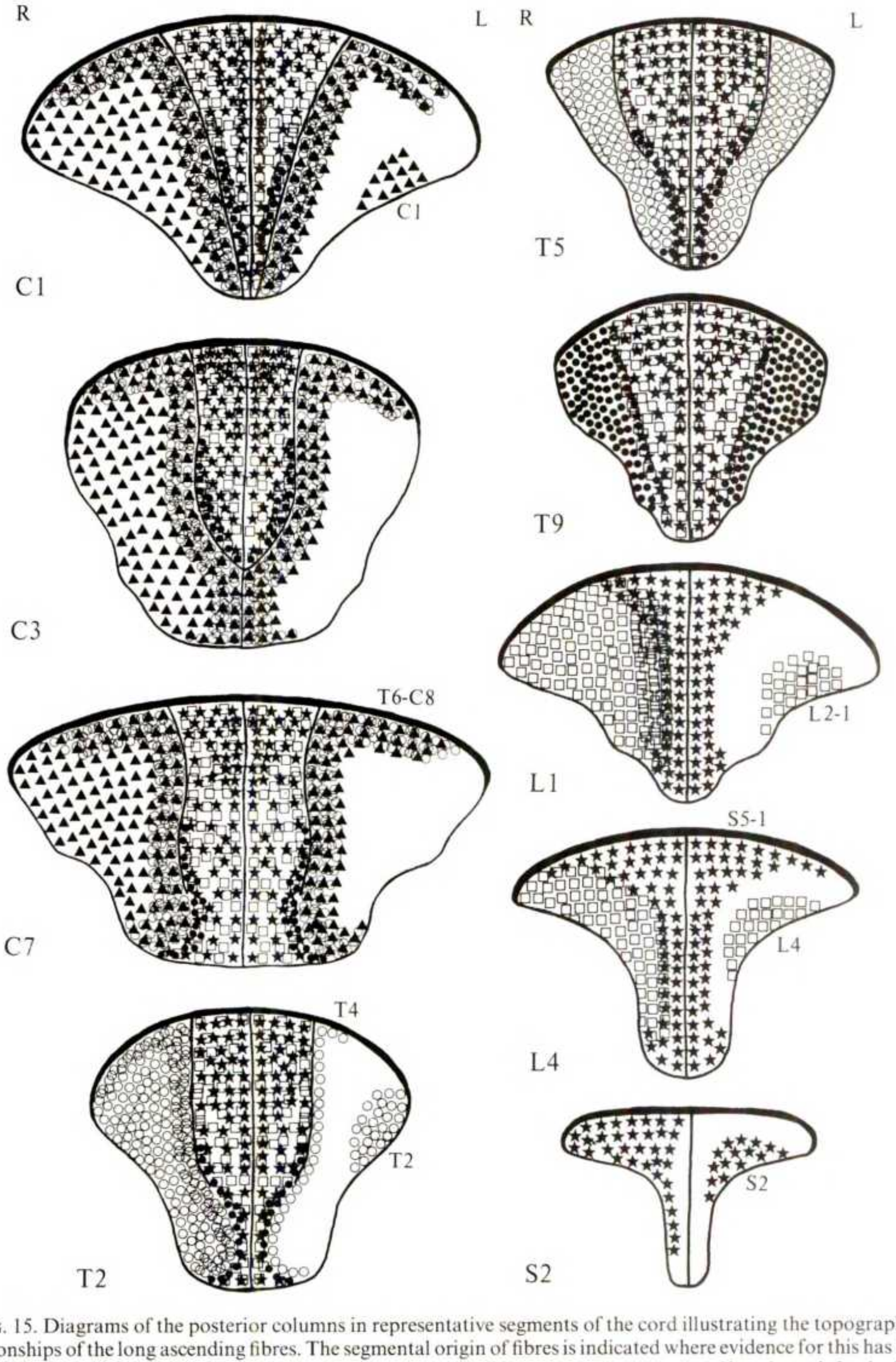


FIG. 15. Diagrams of the posterior columns in representative segments of the cord illustrating the topographical relationships of the long ascending fibres. The segmental origin of fibres is indicated where evidence for this has been given in the paper, labelled on left. On the right, the presence of the other long ascending fibres in each fasciculus is simply indicated. ▲ = cervical. ○ = upper thoracic. ● = lower thoracic. □ = lumbar. ★ = sacral.

(Tooth, 1885; Collier and Buzzard, 1903; Foerster, 1936; Glees and Soler, 1953; Soler, 1958).

We have shown that the shape of the FG in transverse section is different in, and characteristic of, each of the cervical and upper thoracic segments. The shape is so constant in our material that we consider it justified to use our series of photographs as guides in estimating the approximate location of the lateral border of the FG in cases in which the FG and the FC cannot be distinguished from each other. The topographical arrangement of the long ascending fibres in the posterior columns, in different representative segments, deduced from all our cases, is shown diagrammatically in fig. 15.

ACKNOWLEDGEMENTS

We wish to acknowledge our gratitude to Dr J. T. Hughes who has given us the opportunity to do this work in his laboratory, and to the Medical Research Council, who supported it. We also want to thank all the neuropathologists, neurosurgeons and neurologists who have generously provided us with the cases on which this histological study was made.

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(*Received May 19, 1983. Revised December 15, 1983*)

Brain (1984), **107**, 699–726

THE PATHOPHYSIOLOGY OF ACUTE EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN THE RABBIT

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SUMMARY

Clinical, histological and electrophysiological studies were performed on rabbits with acute experimental allergic encephalomyelitis (EAE). The clinical features were similar to those previously described, with the notable exception of the new findings of areflexia, respiratory slowing and hypothermia. The histological findings were also similar to those previously reported, with inflammatory demyelinating lesions both in the central and peripheral nervous system, especially the dorsal root ganglia.

Electrophysiological studies performed one to nine days after the onset of neurological signs demonstrated conduction block in a high proportion of the large diameter afferents in the lumbosacral and thoracic dorsal root ganglia. Single fibre studies with spike-triggered averaging confirmed the conduction block in the dorsal root ganglia. That the conduction block was due to demyelination was indicated by slowing of conduction in large diameter fibres, normal conduction in unmyelinated fibres and the specific effects of temperature and of the potassium channel blocking agent, 4-aminopyridine. These conduction abnormalities in the peripheral nervous system, focused on the dorsal root ganglia, account for the postural disturbance, hypotonia, ataxia and areflexia in rabbits with EAE. Such conduction block is likely to mask the expression of any lesions of the central nervous system that alone could produce similar signs. The implications of these findings for the human demyelinating diseases are discussed.

INTRODUCTION

Experimental allergic encephalomyelitis (EAE), an autoimmune demyelinating disease, has been widely studied as a possible model of multiple sclerosis (MS). This approach has been criticized as EAE is typically a monophasic illness, in contrast to MS which usually has a chronic relapsing or chronic progressive course (Raine, 1976). This criticism has been overcome by the development of chronic relapsing EAE (Wiśniewski and Keith, 1977; Lassmann and Wiśniewski, 1979). Nevertheless there is one aspect of EAE that has been almost entirely neglected, namely, its pathophysiology. Although it is widely assumed that the neurological signs of EAE are due to CNS lesions, two lines of experimental evidence raise strong doubts about this assumption. First, histological involvement of the PNS has been described in all species examined, including the rabbit (Waksman and Adams, 1955; Wiśniewski *et al.*, 1969), guinea pig (Freund *et al.*, 1947; Waksman and Adams, 1956), mouse (Waksman and Adams, 1956) and monkey (Ferraro and Roizin, 1954). Involvement of the PNS also occurs in rabbits with chronic EAE (Raine *et al.*, 1969) and guinea pigs, rats and mice with chronic relapsing EAE (Madrid and Wiśniewski, 1978; Lassmann *et al.*, 1980; Brown *et al.*, 1982). Surprisingly, the functional consequences of these lesions in the PNS have been totally ignored, and the belief that the neurological signs are due to CNS lesions has remained unchallenged. Secondly, there have been many reports of clinical signs of EAE occurring in the absence of CNS lesions, although after a comprehensive review of the literature Levine *et al.* (1975) regarded these observations as invalid.

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The above considerations lead inevitably to the question as to how far the neurological signs in these animals are due to PNS lesions. Very few electrophysiological studies have been directed towards this question. Whereas Lumsden *et al.* (1975) found sciatic nerve conduction velocity to be normal in guinea pigs with EAE, Kaeser (1962) and Kaeser and Lambert (1962) reported it to be reduced. The latter workers attributed their findings to the known histological involvement of peripheral nerve in EAE in this species (Waksman and Adams, 1956).

The importance of determining the site and nature of the lesions responsible for the clinical signs in EAE is threefold. First, if the PNS lesions contribute significantly to the clinical signs, then remyelination of such lesions could be responsible for recovery, and hence the validity of chronic relapsing EAE as a model of MS would need to be questioned. Secondly, the suppression of, or improvement in, the clinical signs of EAE by such agents as myelin basic protein (Alvord *et al.*, 1965) and immunosuppressants (Levine and Sowinski, 1980) provides the basis for their use in the treatment of MS. Thirdly, a knowledge of the site and nature of the lesions responsible for the neurological signs of EAE would add an important dimension to the study of EAE as an autoimmune neurological disease in its own right.

We have therefore undertaken a clinical, histological and electrophysiological study of acute EAE in the rabbit. Acute EAE was chosen because this stage of the disease is common to both acute and chronic relapsing EAE and because an understanding of its pathophysiology would allow the relapses of chronic relapsing EAE to be viewed in perspective. The specific aims of the study were (1) to establish that the disease we induced was typical of acute EAE in the rabbit; (2) to analyse critically the clinical and histological features, in order to determine to what extent such analyses *per se* could elucidate the site and nature of the lesions responsible for the neurological signs; (3) to study nerve conduction in the PNS, including the roots and dorsal root ganglia, in order to determine the functional consequences of the PNS lesions; and (4) to correlate the clinical, histological and electrophysiological observations. A preliminary report has already been published (Pender and Sears, 1982).

MATERIALS AND METHODS

Rabbits

New Zealand white male rabbits, obtained from one source, were aged between 4 and 6 months on arrival and weighed 2 to 3 kg. They were kept individually and fed water and rabbit-guinea pig pellets *ad libitum*.

Preparation of Inoculum

Each batch of inoculum was prepared by mixing 5 g of rabbit spinal cord (after removal of the nerve roots) with 7 ml of incomplete Freund's adjuvant (Difco), 125 mg of H37RA heat-killed *Mycobacterium tuberculosis* (Difco) and 3 ml of 0.9 per cent saline.

Inoculation Procedure and Management of Inoculated Animals

An interval of about seven days elapsed between arrival and inoculation. All except 2 animals weighed between 2.5 and 3.5 kg at the time of inoculation, which was by the intradermal injection of 0.1 ml of inoculum into each of four sites in the nuchal region, chosen in preference to the footpad in order to avoid the possibility of foot pain interfering with the assessment of motor function. Inoculated animals were examined and weighed every second day for the first ten days, and daily thereafter. *Ataxia* was graded as (1) mild, when noticeable on turning or on stopping suddenly after hopping, but with little interference with hopping in a straight line; (2) moderate, with impairment of hopping in a straight line; and (3) severe, with inability to hop. *Weakness* was graded as (1) mild with slight dragging of limbs when hopping; (2) moderate, with weakness of intermediate grade between mild and severe; and (3) severe, with severe weakness and virtually no movement.

During the first few days of the illness, rabbits were often given small amounts of cabbage to promote their appetites. As the illness progressed, more severely affected animals were given daily intraperitoneal or subcutaneous injections of 50 ml of a dextrose-saline solution (4 per cent dextrose; 0.18 per cent saline) and 25 ml of 0.9 per cent saline to minimize dehydration from reduced drinking. Of those animals that developed clinical signs, 25 were anaesthetized and underwent electrophysiological studies in terminal experiments one to nine days after the onset of signs. At the end of the electrophysiological recordings 3 rabbits were perfused with fixative for histological examination. In 2 others subjected to electrophysiological experiments the ganglia studied were removed at the end of the experiment and immersed in fixative. Of the remaining affected animals, 5 were anaesthetized with 25 per cent urethane i.v. and perfused with fixative for histological examination. Six were anaesthetized and underwent lumbosacral laminectomy but died without an electrophysiological study being performed. The remainder were sacrificed by the i.v. injection of urethane or pentobarbitone sodium, either at the height of the illness or after a period of spontaneous recovery.

Controls

Five normal rabbits, observed and weighed for periods of at least one month, served as clinical controls, 2 of these also serving as controls for electrophysiological experiments and 1 for histology. An additional 5 normal animals served as controls for electrophysiological experiments and 1 other normal rabbit as a second control for histology.

Histological Studies

The animals were perfused through the left ventricle with 100 to 200 ml of 0.9 per cent saline followed by 1.2 l of fixative. In 1 control animal and 4 clinically affected animals, modified Karnovsky fixative (2.5 per cent glutaraldehyde and 2 per cent paraformaldehyde in 0.1 M sodium cacodylate buffer, pH 7.4) was used; in 1 normal animal and 1 animal with EAE the fixative was 10 per cent formol calcium and in the remaining 3 animals with EAE, 10 per cent formol saline. The brain, optic nerves, spinal cord with attached roots and dorsal root ganglia (DRG), lumbosacral spinal nerves, left lumbosacral plexus and left sciatic nerve were removed and immersed in fixative. The tissues perfused with formol saline or formol calcium were embedded in paraffin wax and sections stained with haematoxylin and eosin. Tissue perfused with Karnovsky fixative was immersed in this fixative, postfixed with 1 per cent osmium tetroxide, and semithin sections (0.5 μm, Araldite embedding) stained with toluidine blue.

Electrophysiological Studies

Preparation of animals for recording. Anaesthesia was induced by urethane (25 per cent in 0.9 per cent saline, i.v., 7 ml/kg) and supplemented by 25 per cent urethane (0.5 ml/kg i.v.) or pentobarbitone sodium (4 mg/kg). Animals breathed spontaneously through a tracheostomy. During the experiment 100 to 200 ml of either 0.9 per cent saline or Hartmann's solution (compound sodium lactate BP, Travenol) were given slowly by parenteral injection.

Experiments on the lumbosacral region. The animal was mounted in an animal frame (Transvertex). A laminectomy was performed from the fifth or sixth lumbar to the second sacral vertebra, and the left S1, and sometimes L7 and S2, dorsal root ganglia and spinal nerves were exposed. A pool was made with the skin flaps and the dura opened. The left hindlimb was extended and supported in a horizontal position, the left sciatic nerve and gastrocnemii exposed, and a pool formed with skin flaps. The sciatic nerve in the midthigh was dissected free, care being taken to avoid damage to its blood supply. The peroneal nerve was cut in the popliteal fossa. The tissues were covered in paraffin oil. The sciatic nerve and laminectomy pool temperatures were maintained at 37° C by a D.C. heating element in the sciatic nerve pool and a controlled radiant heat lamp. The sciatic nerve in the midthigh was lifted away from the volume conductor and placed across a pair of silver stimulating electrodes 5 mm apart. Since the rabbit sciatic nerve is very susceptible to ischaemia, its continuity was usually maintained. For the C and A delta fibre studies, however, which were performed after the large diameter fibre studies, the nerve was cut and the proximal end stimulated. Stimuli were 0.1 ms square-wave voltage pulses except for the C and delta fibre studies when 1 ms pulses were used. The stimulation rate was 1.0 Hz except for the studies on C and delta fibres when it was reduced to 0.1 Hz to provide good stability of the responses.

All recording electrodes were connected by driven shielded leads to FET source-followers, thence to a preamplifier (band width limited to 1.6–3000 Hz) and then for display on an oscilloscope. Oscilloscope traces were photographed for measurements. Conduction velocities were calculated after allowing for a utilization time of 0.1 ms (Blair and Erlanger, 1936). The area under the curve of the compound action potential was derived by tracing the photographed curve on a digitizer tablet linked to a MOP AM-03 image analyzer (Kontron), coupled to a microcomputer (Research Machines 380Z).

The compound action potential of the left medial gastrocnemius muscle was recorded with a 'belly-tendon lead' through two 21-gauge hypodermic needles, one in the centre of the muscle belly and the other near the Achilles tendon.

For monophasic recording from the distal cut end of the left S1 dorsal or ventral root, the filaments of the root were carefully identified, tied together close to the root entry or exit zone and cut proximal to the tie. The distal cut end was lifted away from the volume conductor into oil and placed on a pair of platinum wire electrodes 4 mm apart. Care was taken not to stretch or kink the root. For all recordings in the present study, negativity at the active electrode gave an upward deflection on the oscilloscope. Volume conductor recordings were made in turn over the left S1 spinal nerve or ventral primary ramus (subsequently referred to as the spinal nerve) 3 to 6 mm from the midpoint of the DRG, over the left S1 DRG and over the left S1 dorsal root entry zone (*see* diagram in fig. 6). The active electrode was a length of 0.5 mm diameter platinum wire insulated to its tip. A platinum reference electrode was placed on nearby bone. Before all recordings any accumulated CSF or other body fluid was aspirated.

At the end of the experiment the dissection was extended to expose the left lumbosacral plexus and the entire length of the conduction pathway from the sciatic nerve to the relevant dorsal root ganglia. The contribution of the spinal nerve, of the segment or segments studied, to the sciatic nerve was confirmed. The L7 and S1 spinal nerves always contributed to the sciatic nerve; the S2 spinal nerve usually but not always contributed. The L6 spinal nerve was not exposed routinely but was noted to give no contribution in some animals and a small or moderate contribution in others. The contribution of S2, when present, and that of L7 varied in size whereas the S1 contribution was always large. The S1 segment was therefore chosen as the standard one for recordings. Conduction distance was measured as the length of a thread placed along the conduction pathway.

Experiments on the thoracic region. A lower thoracic laminectomy was performed and three to five of the T6 to T10 dorsal root ganglia and spinal nerves were exposed. One of the respective internal intercostal nerves was exposed, freed, tied and cut just distal to the tie (*see* Sears, 1964, for anatomical details). For recording the compound action potentials the stimulating and recording procedures were the same as those used in the lumbosacral experiments.

Single fibre studies. Conduction in single afferent fibres was studied by spike-triggered averaging as described by Kirkwood and Sears (1975). Afferent discharges were recorded from the external intercostal nerve or an internal intercostal nerve filament 'in-continuity'. The discharges of a single afferent were selected with a spike discriminator (Digitimer D130) to provide a trigger for averaging the volume conductor recordings over the respective spinal nerve (2 to 4 mm from the midpoint of the DRG), DRG, dorsal root and dorsal root entry zone. The recording arrangements are illustrated schematically in fig. 11. To obtain the trigger spike, the intercostal nerve or filament was freed and lifted away from the volume conductor by two small pieces of polyethylene tubing inserted underneath the nerve. The active electrode was a platinum wire touching the nerve midway between the pieces of tubing. A platinum wire placed nearby on non-nervous tissue served as the reference electrode. The signal was amplified (band width 50–10000 Hz) and fed to a spike discriminator through a second high pass filter (time constant 2 ms), which was needed to provide good baseline stability of the trigger pulses. The volume conductor recordings over the spinal nerve, DRG, dorsal root and dorsal root entry zone were amplified (band width 50–10000 Hz) and averaged with a transient recorder (Datalab DL905) and signal averager (Datalab DL 4000B).

RESULTS

Clinical Findings

An animal was only considered to have EAE if it had neurological signs; weight loss alone was not regarded as sufficient evidence. The day of onset therefore refers to that of the neurological signs. Of the 51 animals inoculated, 41 developed EAE. Two others died from intercurrent infection in the first seven days after inoculation. The remaining 8 did not develop neurological signs during postinoculation periods ranging from 32 to 84 days. The mean day of onset after inoculation was 20 ± 6.4 (± SD) with a range of 12 to 53 days. Only in 1 rabbit did the day of onset exceed 30, and this was one whose age (18 months) and weight (4.75 kg) were much greater than those of the others at the time of inoculation.

Usually the neurological signs evolved over three to four days, were symmetrical and associated with weight loss. Lateral splaying and ataxia of the hindlimbs usually developed first. Hypotonia, loss of the knee jerks and forelimb involvement followed. As the disease progressed, impaired nociception, weakness of the limbs, perineal soiling, paradoxical breathing and slowing of respiration then developed. Thus the clinical findings were generally similar to those previously reported (Morrison 1947; Waksman and Adams 1955, 1956) with, however, the addition of the three previously unreported features of areflexia, hypothermia and slowing of respiration.

Areflexia. In 33 affected animals the knee jerks were absent bilaterally. In 4 others, at least one knee jerk was depressed or absent; in the other 4 the knee jerks remained normal.

Hypothermia. In the normal controls the rectal temperature ranged from 39.0° C to 40.0° C with a mean of 39.4 ± 0.3° C and in 22 rabbits with EAE it ranged from 36.5° C to 41.5° C with a mean of 39.2 ± 1.2° C. The lower and upper limits of normal were taken as the mean ± 2 SD (38.8° C and 40.0° C). Of the rabbits with EAE, 11 had temperatures within these limits, 7 had temperatures below 38.8° C and 4 had temperatures above 40.0° C. All 7 rabbits with temperatures below 38.8° C had severe hindlimb ataxia or weakness.

Slowing of respiration. In 9 normal awake rabbits the resting respiratory rate ranged from 94/min to 170/min, with a mean of 144 ± 23/min. The lower limit of the normal respiratory rate was taken as the mean −2 SD (namely, 98/min). The respiratory rates were counted in 38 animals with EAE, and in 26 of these the rate fell below 98/min during the clinical course. Almost invariably in these animals the rate was normal on the day of onset and fell progressively as the neurological signs increased. The range of the lowest respiratory rate recorded in these animals was 24 to 88/min (mean 61/min).

All animals remained alert throughout the illness and no epileptic seizures were observed. The pupillary and blink responses to light were normal in all.

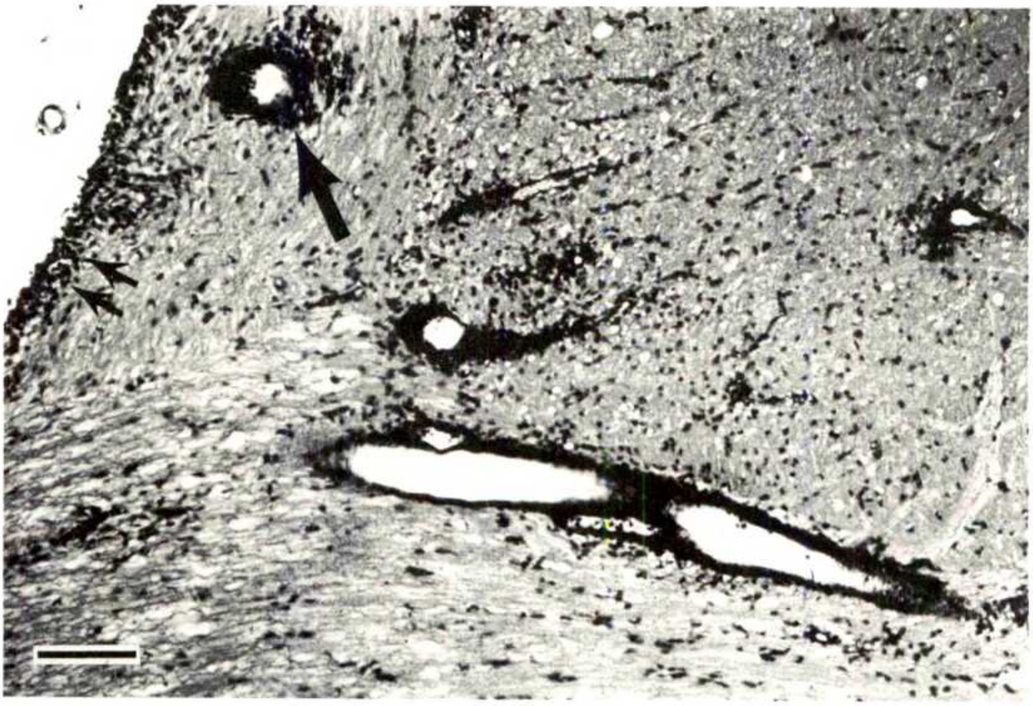

FIG. 1. Transverse section through the brainstem of a rabbit with EAE, four days after the onset of neurological signs. There is extensive perivascular cuffing and para-adventitial infiltration with mononuclear cells (large arrow) as well as meningeal and subpial infiltration with mononuclear cells (double arrows). Paraffin section, H and E stain. Bar = 100 μm.

Spontaneous improvement. Fifteen affected animals showed definite spontaneous neurological improvement. This was first evident two to five days after the onset of EAE. The degree of improvement was usually mild or moderate. Only 2 animals recovered completely, and neither of these had been severely affected.

Histological Findings

Controls. Sections stained with haematoxylin and eosin from normal rabbits showed occasional scattered foci of mononuclear cells in the CNS, particularly the cerebral cortex. Such lesions may occur in normal rabbits, and are attributed to infection with *Encephalitozoon cuniculi* (Goodpasture, 1924; Waksman and Adams, 1956). Semithin sections stained with toluidine blue showed no evidence of demyelination and no other abnormality.

Animals with EAE. Sections stained with haematoxylin and eosin from rabbits with EAE showed widespread meningeal and subpial infiltration with mononuclear cells and some eosinophils, and widespread perivascular cuffing and para-adventitial infiltration with such cells throughout the CNS, especially in the brainstem (fig. 1) and spinal cord. These lesions were most pronounced in the dorsal root entry and

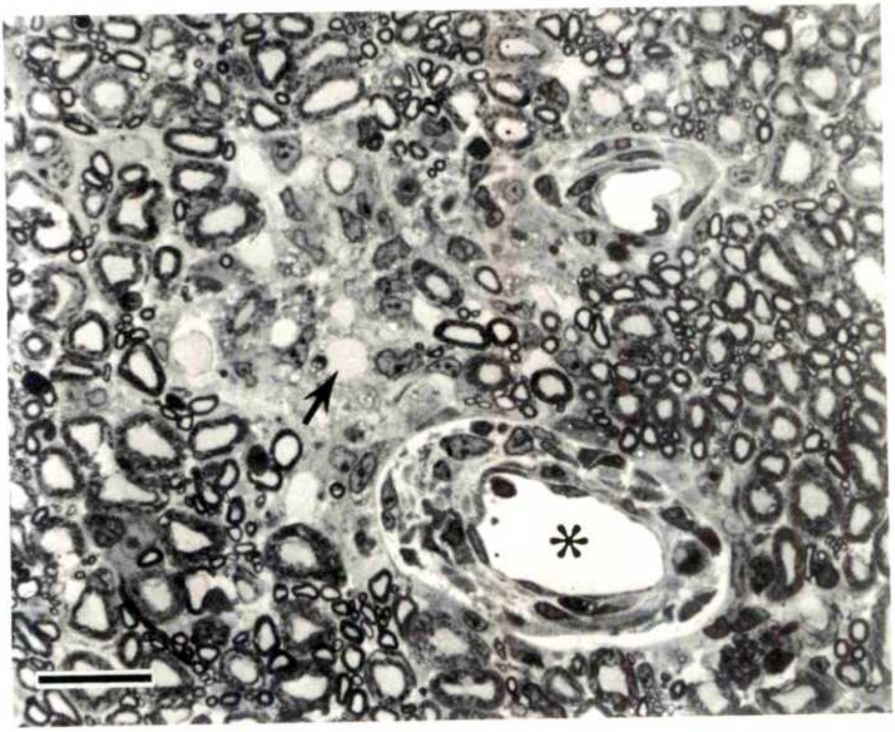

FIG. 2. Transverse section through the dorsal column of the lumbar spinal cord of a rabbit with EAE, four days after the onset of neurological signs. Two perivascular lesions (asterisk in one vessel) have become confluent. Mononuclear cells are present in the Virchow-Robin spaces and in the adjacent neural parenchyma. Demyelinated axons (arrow) can be seen within the region of mononuclear infiltration. Araldite section, toluidine blue stain. Bar = 25 μm.

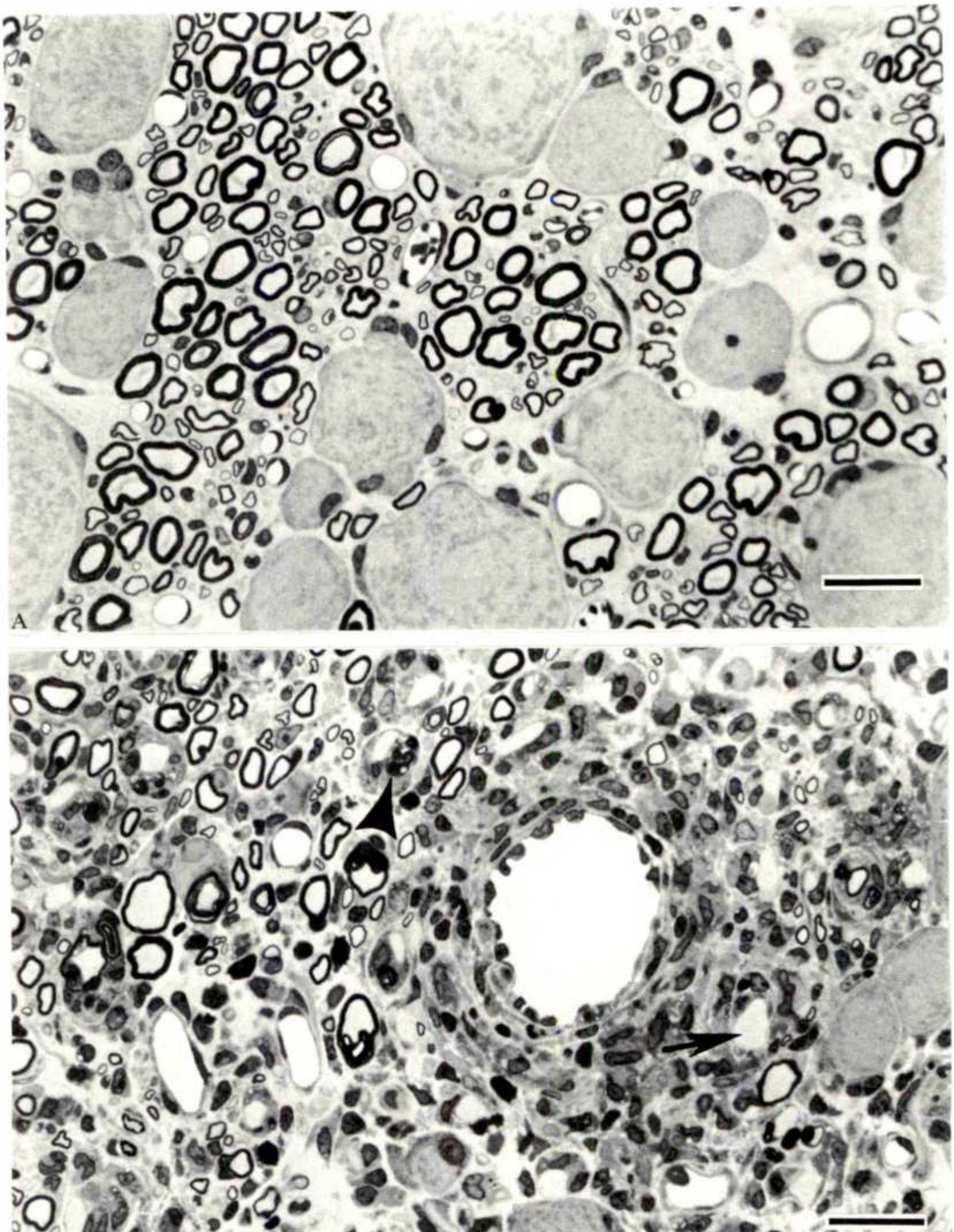

FIG. 3. A, Transverse sections through the S1 dorsal root ganglion of a normal rabbit and B, through that of a rabbit with EAE, two days after the onset of neurological signs. B shows a blood vessel surrounded by a large cuff of mononuclear cells which are invading the parenchyma. There are many demyelinated axons (arrow) within the region of mononuclear infiltration, and intracellular myelin debris (arrowhead) is visible. Araldite sections, toluidine blue stain. Bars = 25 μm.

ventral root exit zones. The anterior horn cells and other neurons in the CNS were normal. Semithin sections of the spinal cord stained with toluidine blue showed mild demyelination strictly confined to the regions of subpial and perivascular mononuclear infiltration (fig. 2), including the dorsal root entry and ventral root exit zones. Myelin debris was prominent within macrophages in the lesions, and plasma cells were occasionally seen among the infiltrating cells. Axons were preserved.

The region most consistently and severely involved was the DRG. Cervical, thoracic and lumbosacral DRG were all affected and lesions were present in every ganglion examined. The lesions again consisted of perivascular cuffing and para-adventitial infiltration with mononuclear cells and eosinophils. Semithin sections showed demyelination in all the ganglia examined (*see* fig. 3). This was often extensive but was always limited to the regions of mononuclear infiltration. There was abundant myelin debris within macrophages, and plasma cells were occasionally present among the infiltrating cells. Axons were normal. The DRG neurons were usually normal. In contrast to the DRG, the spinal nerves were only mildly involved (*see* fig. 7).

Sections of the dorsal and ventral roots showed perivascular lesions similar to those in the DRG, but usually less frequent and less extensive. Sciatic nerve sections were either normal or showed minimal involvement.

Electrophysiological Findings

Conduction in motor nerve fibres. To assess motor nerve conduction and neuromuscular transmission in animals with EAE, the compound action potential evoked in the left medial gastrocnemius muscle by stimulation of the sciatic nerve in the midthigh was examined. In all 16 animals with EAE that were studied, motor nerve conduction and neuromuscular transmission were normal in every respect. To assess motor conduction more proximally, a total of 8 monophasic ventral root recordings were made in 6 animals with EAE. In 5 of these animals the recordings were normal in every respect, both for alpha and gamma fibres (e.g. fig. 4). In the

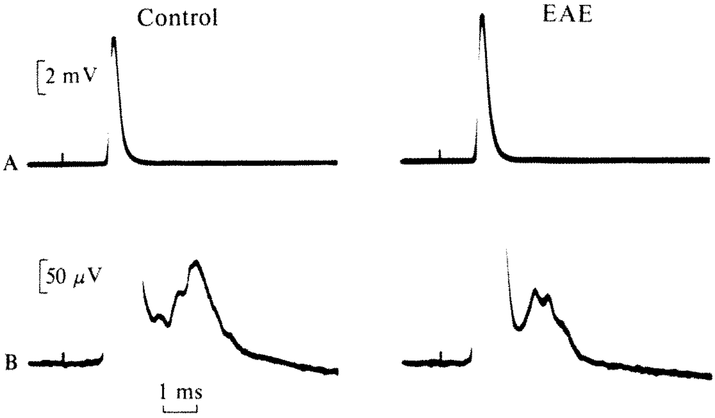

FIG. 4. Monophasic compound action potentials recorded from the distal cut end of the S1 ventral root in a normal control rabbit and in a rabbit with EAE, in response to stimulation of the sciatic nerve. A, maximum A alpha fibre compound action potential. B, maximum A gamma fibre compound action potential. For these and all other recordings, negativity at the active electrode is represented by an upward deflection.

other animal the responses were normal in configuration but severely reduced in amplitude. The most likely explanation for this reduction in amplitude was acute damage to the ventral roots during preparation because, as shown below, when EAE affects nerve conduction, the configuration of the compound action potential is altered.

Conduction in sensory nerve fibres. In contrast to the normal conduction in motor nerve fibres, conduction in sensory nerve fibres from the sciatic nerve to the dorsal root was severely abnormal. All of the 13 dorsal root monophasic compound action potentials from the 9 animals with EAE showed similar abnormalities. Fig. 5A shows typical maximum amplitude responses from a normal control and from an animal with EAE. The response from the latter is greatly diminished in amplitude and has a markedly abnormal irregular configuration replacing the smooth triangular form of the normal response. Compared to a mean of 2.4 mV (range 1.2 to 3.1 mV) for the peak amplitude in the normal controls, the mean in the animals with EAE was 0.4 mV (range 0.08 to 1.1 mV). This reduction would be due to conduction block, temporal dispersion (due to unequal slowing of conduction) or a combination of both. Conduction block was strongly suggested by the areas of the responses and also by measurements of threshold.

The area of the maximum amplitude response in the animals with EAE had a mean of 0.6 mV ms (range 0.1 to 1.3 mV ms) compared with a mean of 1.3 mV ms (range 0.7 to 1.7 mV) in the normal controls. Activation of the same fibres in the sciatic nerve was ensured by using the stimulus giving the maximum amplitude of

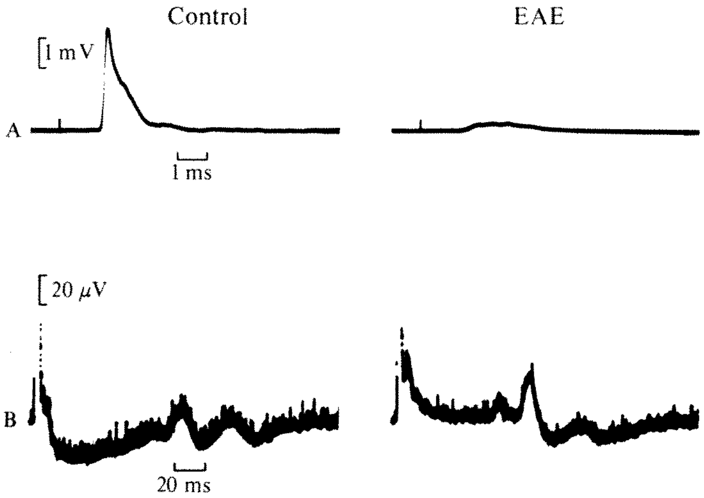

FIG. 5. Compound action potentials recorded from the distal cut end of the S1 dorsal root in a normal control rabbit and in a rabbit with EAE, in response to stimulation of the sciatic nerve. A, maximum A alpha-beta (referred to as 'large diameter' in the present study) fibre compound action potential. B, maximum C fibre compound action potential. Note the different amplitude and time scales.

the negativity in the spinal nerve response, which was normal in the animals with EAE (*see below*). At this stimulus intensity the area of the dorsal root response in the animals with EAE had a mean of 0.4 mV ms (range 0.08 to 0.72 mV ms) compared to a mean of 1.1 mV ms (range 0.9 to 1.33 mV ms) in the normal controls, indicating conduction block in a high proportion of the large diameter afferents in animals with EAE. For simplicity, the term 'large diameter' will be used for fibres whose normal conduction velocity is greater than 25 m/s.

In the normal controls the threshold for the dorsal root response (monophasic recording) was the same as that for the respective spinal nerve response (volume conductor recording). However, in 3 of 5 animals with EAE the threshold for the dorsal root response was increased to as much as 1.5 times threshold for the respective spinal nerve response, indicating conduction block in low threshold large diameter afferents.

At 37° C the conduction velocities of the foot and peak of the dorsal root compound action potential evoked by the stimulus giving the maximum spinal nerve response had means of 64.6 m/s (range 48.9 to 84.3 m/s) and 44.1 m/s (range 32.7 to 55.2 m/s), respectively, in the animals with EAE, compared to means of 89.4 m/s (range 83.2 to 97.9 m/s) and 68.3 m/s (range 63.9 to 75.2 m/s), respectively, in the normal controls. This reduced conduction velocity in EAE could be due to conduction block in the fastest fibres, slowing of conduction, or a combination of both. In some animals with EAE, slowing of conduction was evidenced by the occurrence of delayed components in the dorsal root response at a stimulus intensity giving a normal spinal nerve response.

To determine whether conduction in unmyelinated afferent fibres (C fibres) was affected by the disease, monophasic recordings were made from a total of 9 dorsal roots from 6 animals with EAE. In 8 the C fibre responses were normal in every respect (e.g. fig. 5B). The C fibre compound action potential had three negative peaks with mean velocities of 1.3 m/s, 1.0 m/s and 0.8 m/s, respectively, in the controls and 1.5 m/s, 1.2 m/s and 0.8 m/s, respectively, in the animals with EAE. In fig. 5 the normal C fibre response in the animal with EAE contrasts with the greatly reduced maximum amplitude and the abnormal configuration of the large diameter myelinated fibre response in the same dorsal root recording. Conduction in small diameter myelinated afferents (delta fibres) appeared to be normal in the same roots in which the C fibre response was normal; however, the assessment of delta fibre conduction was limited by the proximity of the delta and large diameter fibre responses. In one dorsal root recording from an animal with EAE, no delta or C fibre response could be elicited. The reason for this is unclear. The large diameter fibre response from this dorsal root showed the typical abnormal configuration and was greatly reduced in amplitude and area.

Localization of the site of conduction abnormalities in afferent fibres. To determine whether the site of the block and slowing of conduction was in the DRG, as anticipated from the histological studies, volume conductor recordings were made over the spinal nerve and DRG in response to stimulation of the sciatic nerve.

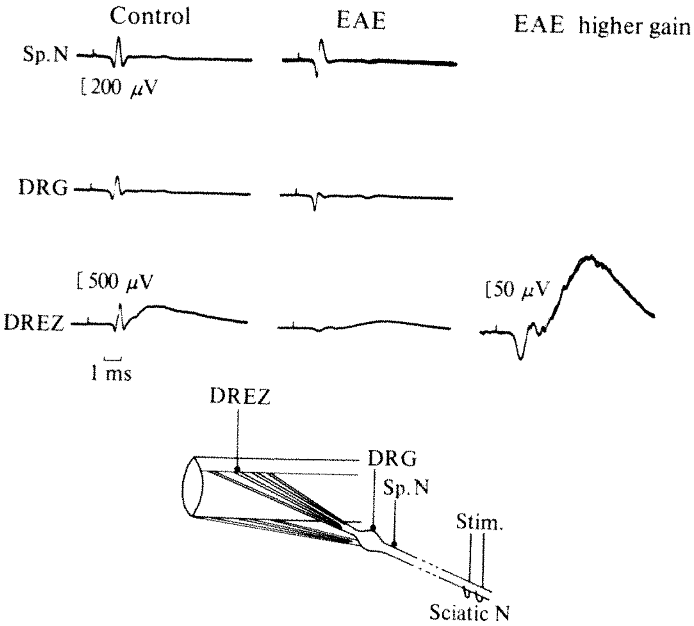

FIG. 6. Compound action potentials recorded, in the volume conductor, over the S1 spinal nerve (Sp.N), dorsal root ganglion (DRG) and dorsal root entry zone (DREZ) in a normal control rabbit and in a rabbit with EAE, in response to stimulation of the sciatic nerve at the intensity giving the maximum spinal nerve response. Note the different gains. The 200 μV calibration bar applies to the spinal nerve recordings and also the dorsal root ganglion recordings. The recording arrangements are illustrated diagrammatically below. Stim. = stimulating electrodes on the sciatic nerve (Sciatic N).

In the normal control the spinal nerve response recorded 3 to 6 mm distal to the DRG consisted of a triphasic wave (positive-negative-positive), the amplitude of the negativity being greater than that of the initial positivity (fig. 6). The initial positivity is due to passive outward current driven by the approaching impulses, while the negativity represents inward current during the rising phase of the action potential under the recording electrode. Recordings were made from a total of 14 lumbosacral spinal nerves in 12 animals with EAE. All recordings were normal in threshold, peak-to-peak amplitude and the conduction velocities of the positive and negative waves (e.g. fig. 6). Also, the ratio of the amplitude of the negativity to that of the initial positivity in the maximum spinal nerve response was normal, with a mean of 1.5 (range 1.0 to 2.3) compared to a mean of 1.4 (range 0.9 to 2.0) in the normal controls. Therefore the normal spinal nerve response in EAE could be used as a reliable index of the population of fibres activated in the sciatic nerve.

The recording over the DRG in the normal control animals was the same as that over the spinal nerve (fig. 6). Recordings were made from a total of 18 dorsal root ganglia from 13 animals with EAE. There was usually a marked decline in the amplitude of the negativity with respect to that of the initial positivity (*see* fig. 6), the mean ratio of the former to the latter at the stimulus intensity giving the maximum spinal nerve response being 0.5 (range 0.2 to 1.0) compared to 1.5 (range 1.0 to 1.8) in the normal controls. The reduction in the negativity indicates that the dorsal root ganglion is the site of the conduction block in the large diameter afferents. This localization corresponds well with the site of the lesions, as illustrated in fig. 7. A normal response was recorded over the S1 spinal nerve where a longitudinal section showed normal myelin sheaths, except for a few small foci of demyelination. In contrast, the recording over the DRG, only 3 mm proximally, shows a markedly abnormal response typical of that described above for EAE, and the corresponding longitudinal section shows extensive demyelination affecting the majority of large diameter fibres.

The proportion of fibres with conduction block in the DRG is likely to be even greater than indicated by the volume conductor recordings over the DRG, because the residual negative wave in these recordings is probably due in part to activity in the subjacent normally conducting ventral root fibres. A large response can be

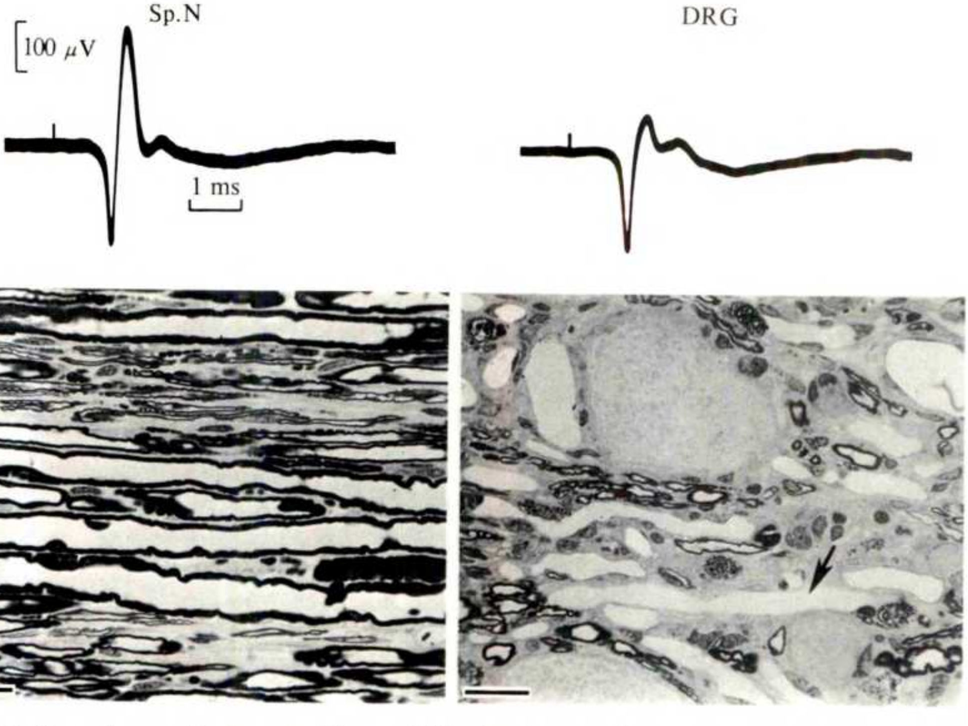

FIG. 7. *Above.* Compound action potentials recorded, in the volume conductor, over the S1 spinal nerve (Sp.N) and dorsal root ganglion (DRG) of a rabbit with EAE, in response to stimulation of the sciatic nerve at the intensity giving the maximum spinal nerve response. The recording sites were 3 mm apart. The experiment was performed five days after the onset of neurological signs. *Below.* Longitudinal sections through the same spinal nerve and the dorsal root ganglion at the sites of the above recordings. The myelin is largely preserved in the spinal nerve, but only 3 mm away in the dorsal root ganglion there is severe demyelination with long stretches of demyelinated axons (arrow) associated with mononuclear infiltration. Araldite sections, toluidine blue stain. Bars = 25 μm.

recorded over the DRG when the distal cut end of the respective ventral root is stimulated.

The lumbosacral DRG was shown also to be the site of slowing of conduction by the demonstration of prolongation of the negative wave in the recording over the DRG (illustrated for a thoracic DRG in fig. 10).

Effects of the conduction abnormalities in the DRG on the afferent volley arriving at the dorsal root entry zone. Conduction from the sciatic nerve to one or more of the lumbosacral dorsal root entry zones was studied by volume conductor recording. The normal response (fig. 6) consisted of an initially positive triphasic wave representing the afferent volley, and a late slow negative wave, the N wave, which is a field potential due to the synaptic currents in the second order dorsal horn neurons excited mainly by low threshold cutaneous afferents. Dorsal root entry zone recordings were made in 14 animals with EAE (24 recordings). The following abnormalities were present (*see* fig. 6). (1) There was a marked reduction in the peak-to-peak amplitude of the triphasic wave, the mean amplitude being 120 μV (range 50 to 400 μV) compared with 740 μv (range 430 to 1000 μV) in the normal controls. This reduction is accounted for by the conduction block in the DRG. (2) There was a gross reduction in the amplitude of the negative component of the triphasic wave, the mean amplitude being 40 μV (range 0 to 190 μV) compared with 550 μV (range 300 to 750 μV) in the normal controls. This reduction is largely accounted for by the conduction block in the DRG, but in part may also be due to conduction block at the dorsal root entry zone in large diameter afferents still conducting through the ganglion. In one animal with EAE, conduction block was demonstrated at the dorsal root entry zone in large diameter afferents that were still conducting, albeit slowly, through the DRG. (3) The conduction velocity of the negative component of the triphasic wave was reduced owing to conduction block and slowing of the fastest fibres in the DRG. (4) The amplitude of the peak of the maximum N wave was reduced, the mean being 320 μV (range 80 to 520 μV) compared to 730 μV (range 630 to 940 μV) in the normal controls. This is most likely to be due to conduction block in low threshold cutaneous afferents in the DRG and possibly at the dorsal root entry zone. (5) The latency to the peak of the N wave was prolonged, the mean being 5.1 ms (range 4.4 to 5.9 ms) compared with 3.3 ms (range 3.1 to 3.4 ms) in the normal controls. In general, the prolongation of the N wave latency was associated more with conduction block than with slowing of conduction in large diameter fibres.

Effects of temperature and 4-aminopyridine on the monophasic dorsal root compound action potential. To determine whether demyelination was responsible for the conduction block in the DRG, the effects of temperature (*see* Rasminsky, 1973) and of the potassium channel blocking agent, 4-aminopyridine (4-AP) (*see* Sherratt *et al.*, 1980; Bostock *et al.*, 1981), on the dorsal root monophasic compound action potential were studied.

The effect of temperature was assessed in 6 animals with EAE. These effects were variable. In 3 animals, there was no effect beyond that seen in the normal control, in 1 a mild effect on amplitude but not on area, in another a mild effect on both amplitude and area and in the sixth animal a marked effect on amplitude and area. The recordings from the last animal were illustrated in a preliminary communication (Pender and Sears, 1982). When the temperature of the laminectomy pool in this animal was increased from 37° C to 40° C, the amplitude and area declined to 48 and 50 per cent of their original values, respectively (*cf* 88 and 74 per cent in the normal control) and when the temperature was reduced to 34° C they increased to 204 and 218 per cent (*cf* 108 and 125 per cent in the normal control). This animal exhibited a reversible increase in the degree of limb splaying and ataxia when its temperature was increased by 1.5° C on the day before the terminal experiment. These physiological and clinical effects of temperature can be accounted for by conduction block occurring in a greater number of demyelinated afferent fibres when the temperature is increased and by restoration of conduction by cooling. Davis and Jacobson (1971) observed similar effects of temperature on the compound action potentials of the peripheral nerves of guinea pigs with experimental allergic neuritis (EAN).

The effects of 4-AP on the compound action potentials recorded monophasically from the dorsal root and in the volume conductor over the spinal nerve were assessed in 2 animals with EAE. Fig. 8 shows the recordings from one. The

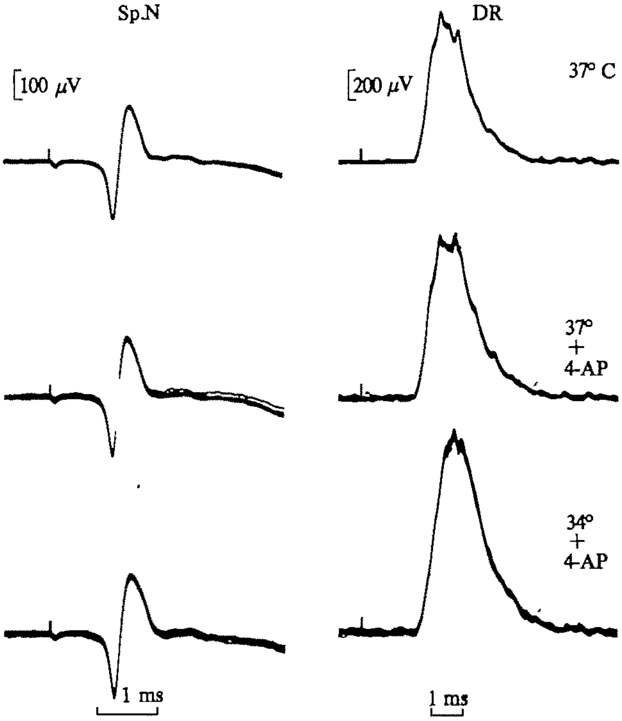

FIG 8 The effect of 4-aminopyridine (4-AP) and of 4-AP combined with lowering of temperature on the compound action potential recorded, in the volume conductor, over the S1 spinal nerve (Sp.N) and monophasically from the distal cut end of the S1 dorsal root (DR) of a rabbit with EAE. For all recordings the sciatic nerve was stimulated at an intensity supramaximal for the amplitude of the dorsal root response.

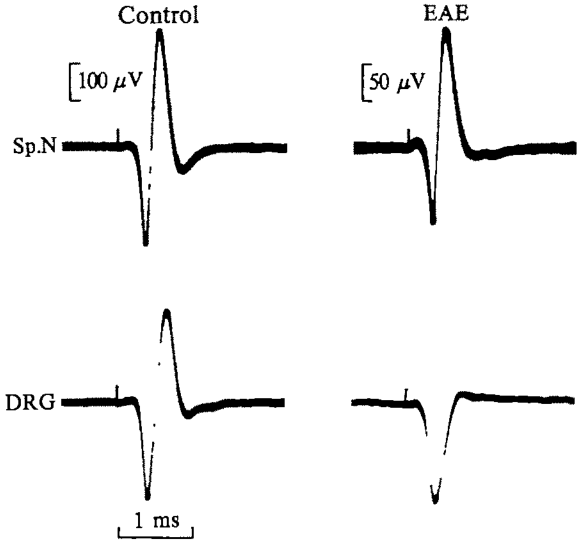

FIG. 9. Compound action potentials recorded, in the volume conductor, over the T10 spinal nerve (Sp.N) and dorsal root ganglion (DRG) in a normal control rabbit and in a rabbit with EAE, in response to stimulation of the respective internal intercostal nerve at the intensity giving the maximum spinal nerve response.

amplitude and area of the dorsal root response had already increased one minute after the intravenous administration of 4-AP and continued to increase with further administration. After 1.25 mg had been given, the amplitude and area of the dorsal root response had increased to 112 and 124 per cent of their original values, respectively, compared with corresponding increases to 103 and 105 per cent for the negative wave of the spinal nerve response (*middle traces*). After the administration of another 1.25 mg of 4-AP, the amplitude and area of the dorsal root response increased to 117 and 136 per cent (not shown). When the temperature was then lowered to 34° C, the amplitude and area of the dorsal root response increased to 138 and 158 per cent of their original values, compared with the corresponding increases to 107 and 123 per cent for the negative wave of the spinal nerve response (*lower traces*). The combined effect of 4-AP and lowering of temperature on the amplitude and area of the dorsal root response was considerably greater than the effect of lowering temperature alone, whereas the combined effect on the amplitude and area of the negative wave of the spinal nerve response was similar to the effect of lowering temperature alone. 4-AP was observed to have similar effects in the other animal with EAE. These effects could be due either to restoration of conduction through the DRG in some fibres or to prolongation of the single unit action potentials at the dorsal root recording site. In either case, paranodal demyelination would have to be present to expose potassium channels, which are absent in the normal mammalian node of Ranvier (Sherratt *et al.*, 1980; Bostock *et al.*, 1981). In view of the histological findings, the effects of 4-AP are more likely to be due to restoration of conduction through the DRG than to an action on fibres at the dorsal root recording site.

Conduction through the thoracic root ganglia. To determine whether conduction was impaired in the dorsal root ganglia of other segments, conduction through the lower thoracic ganglia was also studied. Volume conductor recordings were made over a lower thoracic spinal nerve, DRG and dorsal root entry zone in response to stimulation of the respective internal intercostal nerve in 5 animals with EAE. These studies demonstrated normal conduction from the internal intercostal nerve to the spinal nerve, but conduction block in a high proportion of the large diameter afferents in the DRG (*see* fig. 9). At the stimulus intensity giving the maximum spinal nerve response, the ratio of the amplitude of the negativity to that of the initial positivity in the DRG recording had a mean of 0.25 in the animals with EAE compared with 0.94 in the normal controls. The recordings over the thoracic dorsal root entry zone showed similar abnormalities to those in the lumbosacral recordings. One animal was studied later in the clinical course (six days after onset as opposed to three days or earlier for the other 4 animals) and after it had shown spontaneous neurological improvement. Its recordings (fig. 10), provide clear evidence of slowing of conduction in the DRG. They were made at the stimulus intensity giving the maximum spinal nerve response. In contrast to this response, which is normal, the DRG recording shows a reduction in the amplitude, and also a

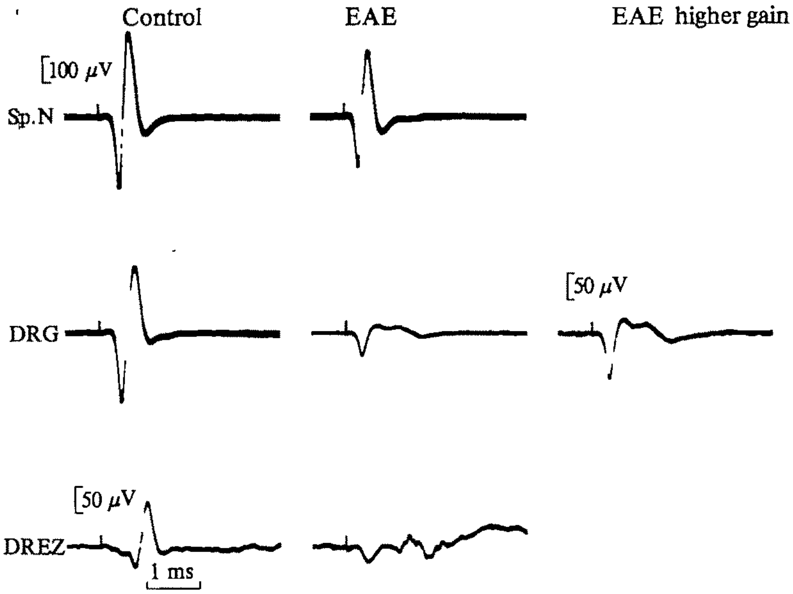

FIG. 10. Compound action potentials recorded, in the volume conductor, over the T10 spinal nerve (Sp.N), dorsal root ganglion (DRG) and dorsal root entry zone (DREZ) in a normal control rabbit and in a rabbit with EAE, in response to stimulation of the respective internal intercostal nerve at the intensity giving the maximum spinal nerve response. The 100 μV calibration bar applies to the DRG recordings in the left and middle column, as well as to the spinal nerve recordings.

prolongation, of the negativity. The difference in the latencies to the ends of the negative waves in the spinal and DRG recordings is 0.6 ms. From this and the distance of 3.5 mm between the recording sites a velocity of 6 m/s was calculated. It is likely that the slowest conduction velocity of the large diameter fibres in the DRG was even lower than this, for two reasons. First, the conduction time for some fibres may have been greater than 0.6 ms, as the large diameter fibres with the slowest velocity in the DRG were not necessarily the slowest large diameter fibres contributing to the spinal nerve response. Secondly, the actual distance over which demyelination had occurred and thus conduction had been slowed in individual fibres was probably less than 3.5 mm. It is likely therefore that the real velocity was in the range of continuously conducting unmyelinated fibres, implying that the demyelinated internodal axonal membrane was now electrically excitable. The dorsal root entry zone recording from the animal with EAE shows an isolated low amplitude positivity and a delayed, predominantly negative, triphasic wave representing conduction through the dorsal root entry zone in fibres conducting slowly through the DRG. Further confirmation of slowing of conduction in the DRG in this animal was provided by the recording of delayed, predominantly negative triphasic waves over the DRG and dorsal root entry zone at threshold for the spinal nerve response.

Single fibre studies. The compound action potential recordings in both the lumbosacral and the thoracic regions have strongly indicated conduction block in a high proportion of the large diameter afferents in the DRG. Nevertheless, they have not provided absolute proof of conduction block, as the reduction in the amplitude and area of the compound action potential could be due to such severe temporal dispersion (due to unequal slowing of conduction) that the slowed responses were hidden in the background noise.

To provide absolute proof of conduction block in the DRG, conduction in single afferent fibres in the thoracic region was studied with spike triggered averaging as described by Kirkwood and Sears (1975). These studies were performed in 2 normal control animals and in 2 animals with EAE. In the normal controls the single fibre potentials recorded over the spinal nerve, DRG, dorsal root and dorsal root entry zone were biphasic (positive-negative) or triphasic (positive-negative-positive) signals, with the negativity always having the greater (greatest) amplitude. The initial positivity is due to the passive outward current generated by activity at the last activated nodes of Ranvier, and the negativity is due to the active inward current occurring during the rising phase of the action potential under the recording electrode. Fig. 11 shows the averaged recordings over the T8 spinal nerve and DRG of an animal with EAE, the trigger spike being provided by a spontaneously firing muscle afferent in the respective external intercostal nerve. The spinal nerve response is a normal biphasic wave, but the response recorded over the DRG 2 mm away is a positive monophasic wave, proving that conduction block has occurred in the DRG. The response over the dorsal root (not shown) was a positive monophasic wave of lower amplitude than that recorded over the DRG, the decline in amplitude being due to the electrotonic decrement in the absence of impulse propagation past the DRG. The single fibre study in the other animal with EAE also showed normal conduction from the external intercostal nerve to the spinal nerve, and conduction block in the DRG.

Correlation between the clinical and electrophysiological findings. There was a good correlation between the severity of hindlimb ataxia on the day of the terminal experiment and the electrophysiological findings, both in the lumbosacral and thoracic regions. Most rabbits with moderate or severe hindlimb ataxia on the day of the terminal experiment had evidence of conduction block in a high proportion of the large diameter fibres in the DRG and at least moderately prolonged N wave latencies. The 3 animals with only mild hindlimb ataxia on the day of the terminal experiment had conduction block in only a small proportion, but slowing of conduction in many of the large diameter fibres in the DRG, and had normal or only mildly prolonged N wave latencies.

There was an even better correlation between the electrophysiological findings and the time interval from the onset of signs to the electrophysiological study. All animals studied one to three days after the onset of signs had evidence of conduction block in a high proportion of the large diameter fibres in the DRG and at least moderately prolonged N wave latencies. The 4 animals studied six or more days after the onset of signs had conduction block in a small proportion, but slowing of conduction in many, of the large diameter fibres in the DRG and normal or only

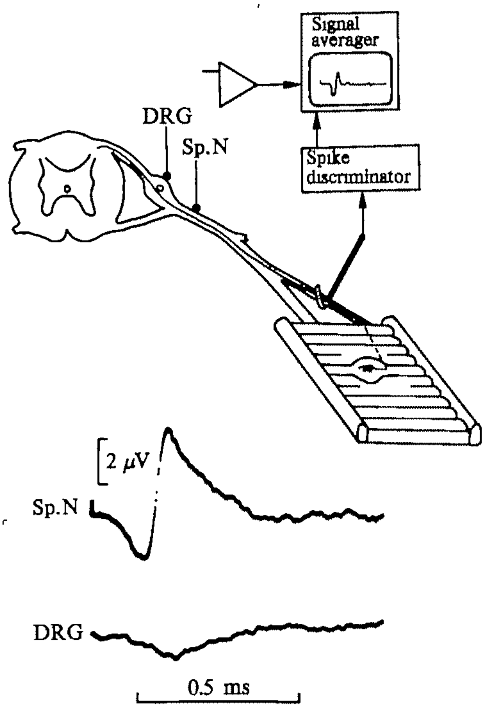

FIG. 11 *Above.* Diagram illustrating the arrangements used for single fibre studies with spike-triggered averaging. Recordings were made from the external intercostal nerve (or from an internal intercostal nerve filament) 'in continuity', and a spike discriminator was used to select spikes arising from a single receptor nerve fibre. These spikes triggered the signal averager, which received its input from volume conductor recordings over the respective spinal nerve (Sp.N) or dorsal root ganglion (DRG). *Below.* Averaged single fibre potentials recorded, in the volume conductor, over the left T8 spinal nerve (Sp N) and dorsal root ganglion (DRG) of a rabbit with EAE. Each recording is the average of 512 sweeps.

mildly prolonged N wave latencies. Three of these 4 animals had shown considerable neurological improvement. Animals studied four or five days after the onset of signs had electrophysiological findings intermediate between those of the animals studied before four days and those of the animals studied after five days.

DISCUSSION

Clinical Findings

EAE developed in 80 per cent of the inoculated animals. The mean day of onset was 20 compared to the mean of 14 found by Waksman and Adams (1955). This difference is probably due to the fact that they induced the disease by intradermal injections into the four footpads simultaneously, which method is much more effective than intradermal injections in the neck (Levine and Wenk, 1961).

The clinical features of weight loss, and of splaying, ataxia and weakness of the limbs are the same as those previously described for EAE in the rabbit. Our findings of areflexia, hypothermia and slowing of respiration are new, areflexia, in particular, being strikingly consistent. Curiously, other workers, with the exception of Morrison (1947), have not mentioned the state of the tendon reflexes in rabbits with EAE. Morrison found that these reflexes were usually present, even sometimes increased, but in one animal they were sluggish, and in another, sometimes difficult to elicit; he also observed clonus in several animals. In the present study the conspicuous and consistent absence of the tendon jerks focuses attention on the functional consequences of the PNS lesions. The hypothermia noted in 7 animals in the present study was probably due to an impairment of thermoregulation caused by autonomic involvement. The increase in body temperature observed in 4 animals may have been due to the autoimmune and tuberculin inflammatory reactions or to intercurrent infection. The slowing of respiration was not due solely to hypothermia, as 8 animals with slowed respiration had normal or increased body temperatures; it may have been due to a lesion affecting the afferent limb of the Hering-Breuer reflexes, perhaps in the nodose ganglion, but this was not investigated. The paradoxical movement of the chest wall observed during respiration indicates intercostal muscle weakness, but physiological studies are required to establish whether its primary cause is a functional deafferentation (*see* Nathan and Sears, 1960; Sears, 1964) or involvement of thoracic motor nerve fibres either in their ventral roots or within the spinal cord (*see below*).

Histological Findings

Our histological findings, including the PNS lesions, are similar to those previously described in rabbits with EAE (Morrison, 1947; Waksman and Adams, 1955, 1956; Wiśniewski *et al.*, 1969). The consistent and severe involvement of the DRG was a striking feature in the present study. In contrast to the paucity of demyelination in the CNS, there was usually extensive demyelination in the dorsal root ganglia. The vulnerability of the rabbit to the lesions of EAE and also to those of experimental allergic neuritis (EAN) was described by Waksman and Adams in 1955, but its functional implications in EAE seem to have been totally ignored.

Functional Deafferentation Due to Conduction Block in the DRG

The compound action potential recordings strongly indicate conduction block in a high proportion of the large diameter fibres in the lumbosacral and thoracic dorsal root ganglia of rabbits with EAE. Absolute proof of conduction block was provided by spike-triggered averaging from single muscle spindle afferents in the respective external intercostal nerve. That the conduction block in the DRG is due to the observed demyelination is indicated by the slowing of conduction in large diameter fibres in the DRG, the normal conduction in unmyelinated fibres and the effects of temperature and the potassium channel blocking agent, 4 amino-pyridine, on conduction. The normal conduction in unmyelinated fibres indicates that axonal damage *per se* is not responsible for the conduction block. The limited effectiveness of 4-AP is accounted for by the requirement that, for 4-AP to restore conduction, potassium channels must be exposed by demyelination of the paranodal region penultimate to the site of conduction block (*see* Sears and Bostock, 1981).

As demyelination causes an impaired ability to transmit a rapid train of impulses (Lehmann and Tackmann, 1970; McDonald and Sears, 1970), it is highly likely that, at physiological firing rates, failure of conduction would occur in those fibres already conducting slowly at the comparatively low rate of stimulation (1.0 Hz) used in the present study. This would contribute to the functional deafferentation.

It is likely that the particular morphology of the pseudomonopolar ganglion neuron confers, on the DRG, vulnerability to the pathophysiological consequences of demyelination. The stem process of the larger ganglion cells consists of a proximal unmyelinated segment followed by short thinly myelinated internodes leading to the branch point (Spencer *et al.*, 1973; Lieberman, 1976). Although a load is presented at the branch point by the stem process and the cell body, it would seem from work on the toad DRG that the safety factor for centripetal conduction through the normal ganglion is maintained high because of the very short internodes of the peripheral process immediately adjacent to the bifurcation (Ito and Takahashi, 1960). It would be expected that demyelination within the ganglion would affect not only the myelin of peripheral and central processes but also that of the stem process. Hence the branch point is likely to be particularly susceptible to conduction block, which perhaps may result from only a minor degree of demyelination.

Because of the conduction block in a high proportion of the large diameter fibres in the DRG, it was usually not possible to determine by orthodromic conduction studies whether the dorsal root and root entry zone were also sites of conduction block for afferent impulses. However, in one animal, conduction block was demonstrated at the dorsal root entry zone in large diameter fibres that were still conducting, albeit slowly, through the DRG.

The severe functional deafferentation resulting from the conduction block in the large diameter fibres in the DRG and to a lesser extent at the dorsal root entry zone accounts for the postural disturbance, hypotonia, ataxia and areflexia in rabbits with EAE. Furthermore, the conduction block in the DRG is likely to mask the expression of any CNS lesions that alone could produce these signs.

The finding of slowed conduction in many large diameter fibres in the DRG at the time of clinical improvement suggests that the improvement is due to restoration of conduction through the DRG. Such restoration could be due either to the development of internodal membrane excitability and continuous conduction (*see* Bostock and Sears, 1976, 1978) or to remyelination. Evidence, suggesting the development of internodal membrane excitability and continuous conduction, was provided in one animal with EAE by the finding of a conduction velocity so slowed as to be compatible with continuous conduction. Remyelination following segmental demyelination is not likely to occur within seven days, as judged by the lysolecithin lesion studied by Smith and Hall (1980), so that the earlier recovery seen in some animals is unlikely to be due to this. On the other hand, lesser degrees of myelin or Schwann cell damage may be repaired more quickly, so recovery by the reconstitution of the myelin sheath remains an open question.

Neurological improvement could also be due to restoration of conduction through the DRG as a result of a fall in body temperature from either a normal or high level, but this possibility was not examined. The electrophysiological studies throw no light on the possible role of CNS functional adaptation in the recovery process.

Weakness

The cause of the limb weakness was not established. The electrophysiological studies exclude a disorder of neuromuscular transmission and any significant lesions in the spinal and peripheral nerves. Furthermore, in two animals with hindlimb weakness, conduction in the distal ventral root was normal, thus excluding significant lesions at this site. These results suggest lesions in a more proximal site as the basis of the weakness. Our finding of demyelination in the region of the ventral root exit zone involving central and peripheral myelin, which confirms the observations by Prineas *et al.* (1969), provides the most likely explanation for the weakness. Such lesions were not assessed electrophysiologically. The paucity of demyelination and of the other parenchymal damage elsewhere in the CNS of these rabbits makes it unlikely that the weakness was of the upper motor neuron type. Finally, the extensive functional peripheral deafferentation due to the lesions in the DRG could also contribute to the weakness (*see* Mott and Sherrington, 1895; Nathan and Sears, 1960).

Impairment of Nociception

The impairment of nociception noted by us is difficult to explain in the light of the findings of normal C fibre conduction and apparently normal delta fibre conduction through the DRG. The most likely explanation is delta fibre conduction block that has been undetected by the electrophysiological studies because of the limited quantitative assessment.

Cause of the PNS Lesions in EAE

Why do PNS lesions occur when animals are inoculated with CNS tissue? When first describing PNS involvement in rabbits with EAE, Waksman and Adams (1955) considered the possibility that the PNS lesions were due to sensitization to PNS antigens from spinal roots contaminating the inoculum. This was not the explanation, as they found PNS lesions when tissue derived solely from the CNS, for example optic nerve, was used. Furthermore, inflammatory demyelinating lesions have since been produced after inoculation with myelin basic protein (Whitaker, 1981). The PNS involvement in EAE has been explained by the finding that the amino acid sequences of the myelin basic protein from the rabbit CNS and of the P_1 myelin basic protein (P_1 protein) from the rabbit PNS are identical (Brostoff and Eylar, 1972), this similarity having also been found in other species including man (Greenfield *et al.*, 1973).

Possible Role of PNS Lesions in Acute EAE in Other Species, in Chronic Relapsing EAE and in the Human Demyelinating Diseases

EAE. It is highly likely that PNS lesions play an important role in the production of neurological signs in acute EAE in other species and in chronic relapsing EAE because (1) PNS lesions have been described in acute and chronic relapsing EAE in all species examined (*see* Introduction); (2) the neurological signs are such as could be accounted for by PNS lesions.

It is important to note that the distribution of PNS lesions in EAE varies with the species. In contrast to rabbits, guinea pigs show greater involvement of the peripheral nerves than of the dorsal root ganglia and spinal roots (Waksman and Adams, 1956). Involvement of the PNS, particularly the peripheral nerves, could account for the severe paraparesis or tetraparesis in guinea pigs with EAE with only slight or undetectable morphological changes in the CNS (Wiśniewski *et al.*, 1976; Wiśniewski and Keith, 1977).

In chronic relapsing EAE the neurological improvement occurring during the remissions may be due not to restoration of conduction in the CNS, as would appear to occur in MS, but to restoration of conduction in the PNS either by remyelination or by the development of continuous conduction.

Human demyelinating disease. The similarity, if not identity, in humans of the P_1 protein of the PNS to the CNS myelin basic protein (*see above*) has a number of implications for the human demyelinating disease. First, it may explain the PNS involvement in the human analogue of EAE, namely the 'neuroparalytic accidents' following rabies vaccination (McIntyre and Krouse, 1949; Appelbaum *et al.*, 1953). Secondly, it has implications for acute disseminated encephalomyelitis. There is evidence that cell-mediated immunity to encephalitogenic myelin basic protein is a concomitant of this disease and may be important in its pathogenesis (Lisak *et al.*, 1974). If this is the case, PNS involvement would be expected which could possibly account for many of the neurological signs, for example cranial nerve palsies, hypotonia, weakness, ataxia, sensory loss and areflexia, described in this disease (Miller *et al.*, 1956). Thirdly, it has implications for the aetiology of MS. There have been several recent reports of PNS involvement in otherwise typical MS (Hopf, 1965; Calder and Pollock, 1976; Schoene *et al.*, 1976). Further research is needed to establish the frequency and extent of this. If PNS involvement were shown to be common in MS, the implication would be that the target of the immune response, whether a neural antigen, viral antigen, or otherwise, is located in both the CNS and PNS; the target could therefore be myelin basic protein. On the other hand, if PNS involvement were shown to be rare in MS, the implication would be that the antigen is confined to the CNS and therefore unlikely to be myelin basic protein.

In the assessment of nervous system diseases in both humans and experimental animals, CNS lesions should not be regarded as being responsible for the clinical signs unless it has been established that PNS lesions either are absent or could not be responsible for the signs.

Vulnerability of the DRG

In the present study there was morphological and physiological evidence of severe involvement of the DRG. The vulnerability of the rabbit DRG to diphtheritic neuropathy (Waksman *et al.*, 1957), EAN and EAE (Waksman and Adams, 1955) was attributed by Waksman (1961) to the reduction that he observed in the blood-nerve barrier in the DRG. The DRG of other mammalian species also have a reduced blood-nerve barrier to proteins, explained by the fenestrae in, and the open junctions between, the endothelial cells (Olsson, 1971; Jacobs *et al.*, 1976). In the cat with diphtheritic neuropathy the DRG is the major site of demyelination and conduction abnormalities (McDonald, 1963*a*, *b*).

In EAE, access to the DRG not only of circulating protein, in particular antibody and complement, but also cells, in particular lymphocytes and monocytes, must be considered. The actual mechanisms whereby demyelination is produced in animals developing EAE after active immunization are unclear. In the present study the absence of any definite acute (within four hours) effect, on nerve conduction, of EAE sera injected into the peripheral nerve or spinal cord (Pender, 1983) excludes any significant contribution of complement-dependent antibody-mediated immunity, as this mechanism results in acute conduction block (Saida *et al.*, 1979; Sumner *et al.*, 1979). By exclusion, the demyelination in the present study is likely to be caused by antibody-dependent cell-mediated immunity (*see* Brosnan *et al.*, 1977) and/or antibody-independent cell-mediated immunity. As lymphocytes appear to pass through, rather than between, endothelial cells (Marchesi and Gowans, 1964; Åström *et al.*, 1968), the endothelial fenestrae rather than the open intercellular junctions may be the critical factor determining the access of lymphocytes to the DRG.

Thus the DRG has a dual vulnerability: one to the development of demyelinating lesions due to the ineffectiveness of the blood-nerve barrier; the other to conduction block due to demyelinating lesions in the vicinity of the branch point.

The vulnerability of the rabbit DRG to EAE and EAN as well as to diphtheritic neuropathy raises the question as to whether the human spinal ganglion, which is particularly vulnerable to the lesions of diphtheritic neuropathy (Fisher and Adams, 1956), is also vulnerable to inflammatory lesions. The spinal ganglia and roots are certainly involved in acute idiopathic polyneuritis (Asbury *et al.*, 1969), but it is unclear as to whether the ganglia (and roots) show greater histological involvement than peripheral nerve. Involvement of the spinal ganglia and adjacent spinal roots could account for the observations that some patients with diphtheritic neuropathy and some with idiopathic polyneuritis have severe neurological signs but normal peripheral nerve conduction studies (Kurdi and Abdul-Kader, 1979; McLeod, 1981).

Conclusion

It is clear from these results and our survey of the literature that the functional consequences of the well-known PNS lesions in EAE have either been ignored or underestimated. PNS involvement in EAE in general and the dual vulnerability of the dorsal root ganglia described in this work have important implications for the human demyelinating diseases.

ACKNOWLEDGEMENTS

We thank Drs L. Cuzner and C. Bolton for advice concerning the preparation of the inoculum and Miss R. Bashir for technical assistance in the histological study. Dr P. A. Kirkwood is thanked for his criticism of an earlier version of this manuscript. Support by the National Fund for Research into Crippling Diseases and the Brain Research Trust is gratefully acknowledged.

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(*Received August 9, 1983. Revised December 2, 1983*)

Brain (1984), **107**, 727–749

MICROSTIMULATION OF SINGLE TACTILE AFFERENTS FROM THE HUMAN HAND

SENSORY ATTRIBUTES RELATED TO UNIT TYPE AND PROPERTIES OF RECEPTIVE FIELDS

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SUMMARY

Tungsten microelectrodes were inserted percutaneously into the median nerve of alert human subjects for recording and stimulation of single nerve fibres. Impulses from mechanoreceptive units in the glabrous skin of the hand were recorded and single afferents were characterized with respect to unit type (FA I, FA II, SA I, and SA II), as well as size and shape of receptive field, and force threshold.

The electrode was then reconnected to an electrical stimulator and short pulse trains (0.25 to 0.5 s, 20 to 100 Hz) were delivered at successively increasing current intensity, while the subject was asked to report any sensation that he noticed in the hand. The first sensation was always that of a localized skin deformation within a small area, typically 2 to 3 mm in diameter, often coinciding with the receptive field of the recorded unit. Spatial matching was also found in many cases for the size, shape and orientation of the perceptive and receptive fields, strongly suggesting that the sensation was accounted for by the recorded unit that had been selectively activated by the current pulses.

There were clear differences between group data associated with the four types of units with regard to the quality of the percepts. Vibratory sensation was reported with all FA II units and was common with FA I units, whereas a sustained indentation was often associated with SA I units. Indirect evidence suggested that activation of SA II units usually did not elicit a sensation. It was confirmed that a single impulse in a single FA I unit may elicit a sensory response in the attending subject, whereas a much larger input was required from SA I units, which are also less sensitive to mechanical stimuli. This was one of several findings supporting the impression that differential receptive properties, even within a group of afferents, were associated with different sensory responses.

It was concluded that a train of impulses in a single tactile unit may produce within the brain of the subject a construct which specifies with great accuracy the skin area of the unit's terminals as well as a tactile subquality which is related to unit properties.

INTRODUCTION

An ultimate goal in the study of sensory systems is to arrive at an understanding of the mechanisms by which the brain produces useful percepts on the basis of afferent information from sense organs. One approach to this complex sequence is to analyse the relationship between impulse activity in neural elements and the nature of

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associated percepts, with the immediate purpose of defining the laws which the brain must follow when producing the percept. Such studies might shed some light on the phenomena that we introspectively experience as consciousness. Mountcastle and coworkers opened the area of studies of psychoneural correlates at the unitary level with a series of analyses which are now classical (Werner and Mountcastle, 1965, 1968; Talbot *et al.*, 1968; Mountcastle *et al.*, 1969; LaMotte and Mountcastle, 1975). In these studies neuronal events in primary afferents of subhuman primates were related to psychophysical data extracted from human subjects when identical stimuli were delivered in the two species.

Development of the microneurographic technique of recording from single fibres in human nerves (Vallbo and Hagbarth, 1968) has provided a method for analysing psychoneural correlates in the somatosensory system at the unitary level in man. A number of studies using this method have been produced over the last decade (Torebjörk and Hallin, 1972, 1973; Gybels and van Hees, 1972; Franzén and Lindblom, 1976; Hensel, 1976; Järvilehto *et al.*, 1976). In particular, detection and scaling problems in tactile sensitivity have been explored at a quantitative level using adequate stimulation of cutaneous mechanoreceptors (Johansson and Vallbo, 1979*a*; Knibestöl and Vallbo, 1980).

Most tactile stimuli excite a large number of afferent units whose impulses might together constitute the basis of the percept produced in the brain. With natural stimuli it is difficult to define the role of an individual afferent and to assess whether the connections from the sense organ in the skin up to the highest levels of the somatosensory system ever allow an individual afferent unit to account for basic characteristics of a sensation, such as location, quality and duration. In the present study, these questions have been investigated, using electrical microstimulation to activate identified single nerve fibres in man, as first reported by Torebjörk and Ochoa (1980) and shortly afterwards by other groups (Konietzny *et al.*, 1981; Vallbo, 1981). The findings suggest that specific percepts are often elicited by the stimulation of a single afferent of a specific type. A preliminary account has already appeared (Vallbo *et al.*, 1982).

METHODS

The material presented was collected in 20 experiments conducted on 2 female and 18 male volunteers. The age of the subjects varied from 20 to 48 years (27 ± 7, mean ± SD). Most of the subjects were students of medicine and dentistry. They had all given their informed consent to the experiments which were conducted according to the Declaration of Helsinki.

General Procedure

The subject was comfortably seated in a dental chair with his right forearm extended and supported in a moulded vacuum cast. His hand was supinated and rested in a plasticine mould. Unitary impulses from tactile afferents were recorded percutaneously. When the physiological properties of a unit had been determined, trains of electrical pulses were delivered through the recording electrode and the subject was asked to describe his sensation at liminal stimulus intensity. In some sessions the intensity was further increased and any associated change of the subject's perceptive experience was explored.

Psychophysical Tests

Before the nerve recording was initiated, one or two simple psychophysical tests were conducted in order to check that the subject was able to perform adequately in a task of this nature. Stimuli were delivered with von Frey hairs (*see below*) on the pad of the middle finger. In a detection task using a yes–no procedure the thresholds were found to fall in the same range as reported before with an identical stimulus technique (Johansson *et al.*, 1980). Moreover, in 16 subjects a magnitude estimation was conducted using five von Frey hairs ranging from 2 mN to 32 mN. It was found that the subjects performed fairly consistently; the exponents of the fitted power functions ranged from 0.48 to 1.28 (*see* Knibestöl and Vallbo, 1980).

Nerve Recording

Impulses of single afferent units were recorded from the right median nerve, or in one experiment from the ulnar nerve, using the microneurographic method of Vallbo and Hagbarth (1968; for details, *see* Vallbo, 1972). In short, insulated tungsten needle electrodes with a tip diameter of approximately 10 μm were inserted percutaneously 4 to 6 cm above the elbow. The impedance of the electrodes was 100 to 300 kohm at 1 kHz. When a nerve fascicle innervating the glabrous skin of the hand had been impaled, the position of the electrode was carefully adjusted until single unit impulses from a low threshold mechanoreceptive afferent could clearly be discriminated from the background activity. During this searching procedure the experimenter was continually delivering light mechanical stimuli by tapping and stroking the subject's hand with his own hand.

Unit Identification

Units responding to light tactile stimuli were separated into four groups, FA I, FA II, SA I and SA II, according to the criteria previously described (Iggo and Muir, 1969; Knibestöl and Vallbo, 1970; Chambers *et al.*, 1972; Knibestöl, 1973, 1975; Johansson, 1978; Hulliger *et al.*, 1979). The FA I units have previously been denoted RA or QA units, but these terms are unfortunate because such units constitute only one group of rapidly adapting units. The FA II units have previously been denoted PC units, referring to the assumption that the end organs are pacinian corpuscles.

Mechanical Stimulation

A set of von Frey hairs was used to assess the threshold of the units as well as the extent of their receptive fields. The hairs were constructed to produce the following forces when held steadily against the skin: 0.25, 0.5, 1, 2, 4, 8, 16, 32 and 64 mN. Repeated checks revealed that the actual force delivered by a hair was not constant during the experimental period but often somewhat lower than the nominal value. However, the force of any hair was never less than the nominal value of the preceding hair in the series. It has been shown that the peak stimulus force during application does not much exceed the steady state force with properly constructed von Frey hairs (Johansson *et al.*, 1980). In some tests a hand-held device was employed which included a strain gauge system producing a continuous force record.

Assessment of Threshold and Receptive Field

The threshold was defined as the nominal force of the weakest von Frey hair which produced an impulse in about 25 per cent of the tests or more. A four times stronger stimulus was then used to determine the extent of the receptive field. The skin area from which impulses were elicited with this stimulus was carefully mapped and marked on the skin with a fine pen. It has been shown that this method delineates a receptive field which is slightly larger than the area enclosing the end organs of the tactile units (Johannson, 1978). The largest and the smallest diameters of the receptive field as marked on the skin were measured and, in case the shape deviated from round or oval, a drawing of the field was produced and transcribed onto the protocol. For a minority of units the receptive field was more crudely assessed, although the exact location of the approximate field centre was indicated on the skin.

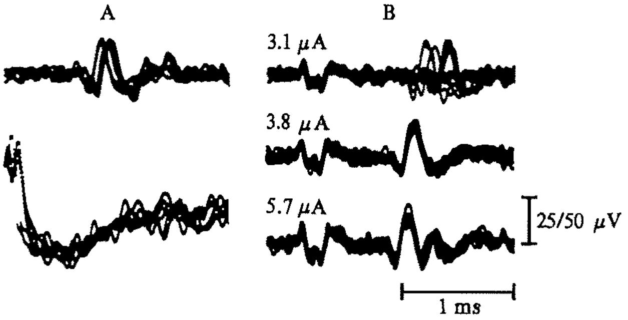


FIG. 1. Single unit stimulation and recording from an exposed cat saphenous nerve. In A, impulses of a fibre were recorded with hook electrodes on the nerve trunk (*upper trace*) and, more distally, with a tungsten needle electrode discriminating the single unit (*lower trace*). The oscilloscope sweep was triggered by the rising phase of the impulse in the lower trace Activity was evoked by mechanical stimulation within the receptive field of the afferent unit. In B, series of stimulating current pulses were delivered through the tungsten needle electrode, the impulses being recorded with the hook electrodes as in A. All-or-none deflections of identical shape and similar latency as in A are present in the upper and middle trace of B, whereas more complex deflections indicating several active fibres appear in the bottom trace when the current intensity was further increased. A number of sweeps (6–15) were superimposed in each record. Amplitude calibration in 25 μV for all but the lower left trace, for which it is 50 μV.

Electrical Stimulation

It was demonstrated in control experiments on exposed cat nerves that it is possible to stimulate electrically the one single fibre whose impulses are discriminated with the recording needle electrode as illustrated in fig. 1. Panel A shows impulses from the same afferent recorded simultaneously at two sites along the nerve, with a pair of hook electrodes on the nerve trunk (upper trace) and a needle electrode discriminating a single unit more proximally (lower trace) (*see* Vallbo, 1976). The oscilloscope sweep was triggered by the latter recording with the result that the initial part of the impulse is not seen. When electrical pulses of liminal intensity were delivered through the tungsten needle electrode (*see* panel B), all-or-none impulses of identical shape and at similar latency as in panel A appeared at the other electrode. When the stimulus was increased slightly, a second impulse of smaller amplitude appeared at a longer latency (panel B, lowermost trace), indicating that a second fibre was recruited. The ratio of stimulus intensity required for the activation of one and two fibres varied between 1.0 and 3.2 (n = 44).

Theoretical considerations as well as actual experiments indicated that positive pulses were most effective in stimulating single nerve fibres. The stimulator which was designed to produce constant current pulses was a battery-powered floating circuit, optoelectrically triggered to produce the desired train of pulses. The shape of the current pulse at the electrode is shown in fig. 2, where it may be seen that it deviated from a perfect rectangular pulse. An initial and short-lasting deflection in the negative direction was produced due to a capacitative cross-talk from the trigger unit. Moreover, the rising phase was slightly curved, largely due to the capacitance of the connecting coaxial wire (fig. 2A). At stimulus intensity above 2 μA, the pulse shape was more seriously distorted such that a plateau was difficult to define (fig. 2B). In this range an approximate mean-amplitude was assessed on the basis of photographs collected in a separate control experiment. Fortunately, the higher range of stimulus intensities (above 2 μA) was used mainly in tests when the exact current intensity was not crucial. Polarization effects which may occur during train stimulation were found to be small or negligible at the rates and intensities employed in the present study. Nevertheless, polarization may have the important effect at near-threshold stimulation of decreasing the probability of excitation. Routinely the pulse train used lasted 0.25 or 0.50 s and was repeated every other second, whereas the pulse rate was between 20 and 100 Hz (20, 25, 40, 50, 80, 100 Hz). In a few tests, other train parameters were also employed, particularly when the purpose was to assess the minimal number of pulses or the minimal pulse rate required to elicit a sensation when a unit was stimulated. The subjects were usually allowed to hear the train of stimulating pulses through a loudspeaker so that they knew when the stimulus was on, except in tests when the effects of train parameters on the percept were studied. In most experiments a stimulus strength of 7.48 μA was not exceeded even when a sensation was lacking at this intensity.

The intensity of the electrical stimuli was successively increased between trains from minimal values until the subject reported a sensation. Care was taken to keep the stimulus at liminal intensity for a sensation in order to minimize the risk of exciting several fibres. This strategy entailed the disadvantage that some pulses in the train might be subthreshold, as was confirmed in control sessions with stimulation and recording from single motor units. Sometimes when near-threshold intensities were employed only some pulses of a train were effective. Stimulus intensity often had to be increased successively during a session in order to continue exciting the fibre.

Assessment of Attributes of Percepts

The subject was first asked to localize the sensation on the skin surface with the aid of a schematic drawing of the hand, where 18 separate skin regions had been labelled. When he had produced the code number for the appropriate region he was asked to describe, in his own words, the location in more detail. The final localization was achieved with a procedure that included alternating electrical stimulation and light mechanical indentation with a glass rod while the subject reported whether or not he felt the two stimuli at the same spot. A convenient switching device and the well-trained cooperation of two experimenters made this procedure fast and smooth. As the receptive field of the afferent unit had already been indicated on the skin with ink it was immediately obvious to the experimenter whether the receptive field of the afferent unit and the perceptive field of the sensation had an identical location, that is, whether a *matching sensation* was present. It should be pointed out that no attempt was made to assess the precise distribution of the sensation with this matching procedure, just the location. If a matching sensation was reported the attributes of the percept were further explored. If not, a schematic analysis was pursued in a limited number of sessions, mainly in order to assess the distance between the receptive field of the recorded unit and the location of the percept. This distance was measured along the skin surface between the centre of the receptive fields and the location of the percept. For two neighbouring finger tips the path *via* the palm was measured.

The attributes of the percept were mainly defined by a set of multiple-choice questions, each one focused on a limited aspect. They were written on charts in bold text, supplemented with schematic drawings, and the charts were successively presented to the subject. One purpose of this design was to ensure the identity of questions between experiments and to avoid ambiguities and bias that could easily be introduced if data were to be extracted from the subjects' verbal accounts. Small modifications were made during the series of experiments to clarify particular points and to refine the logic. The essence of the nine questions is as follows, as well as the alternative answers offered to the subject.

(1) Shape of the skin area where the sensation was present (round, oval elongated, irregular).

(2) Size of the skin area where the percept was present. (The subject was faced with 10 filled circles on the chart with diameters from 1 to 10 mm and he was asked to choose the one which most adequately

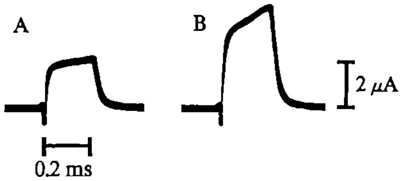


FIG. 2. Shape of current pulse at two intensities recorded over a resistance close to the tungsten needle electrode. Upward deflections indicate positive pulses, i.e. current flowing from the intraneural needle electrode to an extraneural electrode.

matched the size of the percept. When the sensation was felt within an area smaller than 1 mm in diameter two alternatives were offered, 'a small point' or 'a very small point close to the smallest that you can imagine'. In the formal analyses these two alternatives were given the size of 0.1 and 0.01 mm, respectively. When the size of the percept was larger than 10 mm in diameter the subject was asked to give an approximate estimate of the size in mm.)

(3) Is the sensation continuous within the area or is it composed of a number of small points close together (continuous, several points)?

(4) Is the sensation natural or unnatural in the sense that you can imagine a mechanical stimulus which would produce the same sensation (completely natural, almost natural, possibly natural, rather unnatural, completely unnatural)?

(5) Is the sensation felt on the skin surface or below (clearly on the skin surface, slightly below, definitely below, or both on the skin surface and below)?

(6) Is the sensation clearly defined in space (with sharp borders, slightly diffuse, clearly diffuse)?

(7) Is the sensation stationary in space or is there any element of movement along the skin surface (does it grow and/or shrink, does it move from one point or area to another)?

(8) Is the sensation cyclic or noncyclic with regard to intensity during the stimulation period, that is, is there any element of pulsation, vibration, flutter, wobbling or buzzing (cyclic, noncyclic)? The subject was not asked to differentiate between flutter and vibration (*see* Talbot *et al*., 1968).

(9) Quality of sensation. This aspect was explored at two levels which were covered by two questions. The first question gave the following 7 options: (i) touch, pressure, vibration or other mechanical event; (ii) temperature; (iii) tickle; (iv) itching; (v) painful; (vi) sensation of electric current; (vii) any other kind of sensation. These options were split in the next question into a number of subqualities. Some were fairly close synonyms and were introduced to facilitate the subjects' decision rather than to attempt to provide a more sophisticated description. In the final analysis the options within the group of mechanical sensations were condensed into 6 main categories (noncyclic indentation including a single tap, blow, etc., noncyclic pull or pinch, noncyclic pin prick, cyclic indentation, cyclic pull or pinch, cyclic pin prick). Options within the other main groups, that is, temperature, painful, etc., are not of major interest as they were very seldom chosen.

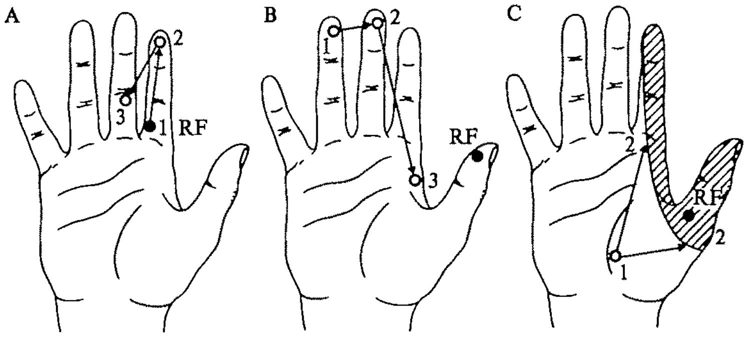
Nonparametic statistics were employed and group data are presented as 'median, 25 to 75 percentile (quartiles).'

RESULTS

Once it had been established that the subject performed adequately in simple psychophysical tests (*see* Methods), recording was initiated from single nerve fibres belonging to mechanoreceptive afferents in the median nerve. As soon as a stable and well isolated unit was found, its functional properties were determined. The recording electrodes were then connected to a stimulator and trains of stimulating pulses were delivered which eventually gave rise to a sensation which the subject was asked to describe.

Effects of Stimulating Current Intensity on the Subject's Percepts

Sample data from three trials in 3 different subjects are illustrated in fig. 3 when the stimulus intensity was successively increased from subliminal values. The first sensation reported was practically always (99 per cent) that of a weak mechanical deformation within a small skin area, typically 2 to 3 mm in diameter. This sensation was not uncommonly located within the receptive field of the unit which had



o/● 1–3 Perceptive field location ● RF: Receptive field location

FIG 3. Sample data demonstrating effects of successively increasing current intensity with intraneural microstimulation. The receptive fields of 3 afferent units in A, B and C, respectively, recorded immediately before stimulation, are indicated by filled circles and RF, whereas the locations of the successively recruited percepts are indicated by open circles, numerals and hatched area. Open circles represent sensation of light mechanical deformation within a small skin area, whereas the hatched area in C represents a paraesthetic sensation Only in A was a matching sensation reported, i e. the percept at liminal intensity coincided with the receptive field, as indicated by the numeral 1 at the filled circle.

been recorded immediately before the stimulation (fig. 3A), although not always (fig. 3B, C). The sensation at liminal strength remained practically invariant when the stimulus was increased in small steps. In a few tests, however, the subject reported that it was very faint and hardly perceivable at liminal strength, but became stronger and more vivid when the stimulus was minimally raised, although its quality and spatial properties did not change. This effect might be related to polarization, producing only a few nerve impulses at liminal current strength. At some higher stimulus level an additional sensation was reported, which was usually also described as light mechanical deformation within a similarly small skin area. However, this area was often located at a considerable distance from the first (fig. 3A, B, C). With a still stronger current another one or two sensations of similar kind sometimes appeared and the subject reported having three or four simultaneous sensations of light mechanical deformation at different points within the hand (fig. 3A, B). The probability for other qualities increased with stimulus intensity, notably painful or paraesthetic sensations. An example is shown in fig. 3C where the second sensation was of paraesthetic nature and extended over a large area that included the receptive field of the unit.

Successive sensations when stimulus intensity was increased did not appear in an orderly manner at increasing distances from the receptive field of the afferent unit but were distributed at random. Fig. 4 shows the distance between receptive field and the location of the first, second and third nonmatching sensation as a function of stimulus intensity. There is no relation between the rank order of the sensation and the distance from the receptive field of the afferent unit, as is obvious from the three sets of symbols covering the same range along the ordinate. Within a particular rank there is no relation between stimulus intensity and distance, as each set of symbols is randomly distributed within an area of the plot. The stimulating current increased with the rank order, although the overlap between stimulus intensities required to produce one, two or three sensations was quite large. The median values for one, two and three sensations were 1.71, 3.29 and 3.83 μA.

For most data points in fig. 4 the sensation had the quality of light and nonpainful mechanical deformation; it was slightly painful or had a paraesthetic character in a minority. Painful sensations were always limited to a small point, whereas paraesthetic sensations extended over much larger areas than did sensations of mechanical deformation.

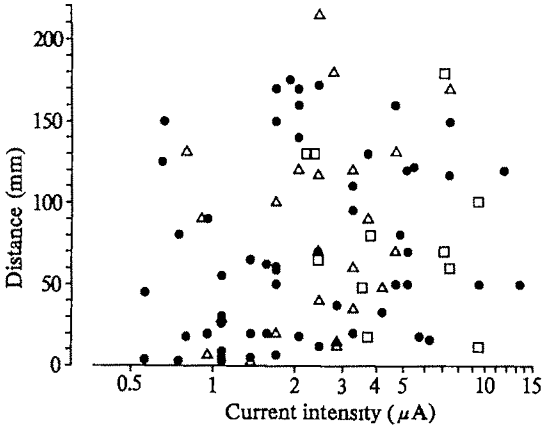


FIG. 4. Distribution of distances between the receptive field of the recorded afferent unit and the successive perceptive fields as a function of stimulus intensity required to produce first, second, and third nonmatching sensation (filled circles, triangles, and squares, respectively). The abscissa is logarithmic in order to compress the scale.

Sensations Attributed to Stimulation of Single Afferent Units

The following sections are devoted to a material collected from 59 recording/stimulation sessions when the subject reported a percept within the receptive field of the afferent unit recorded immediately before. The basic structure of the data collected may best be demonstrated by a few examples. Fig. 5 shows the receptive and perceptive fields associated with 2 units, an SA I and an FA I. The receptive field of the SA I unit was located on the dorsum of the index finger close to the nail as indicated in fig. 5A. It was oval in shape with its long axis oblique to that of the finger. The axes of the field were 2.0 mm and 3.5 mm giving an area of 5.5 mm^2. When the recording electrode was reconnected to a stimulator and a train of pulses at a rate of 50/s delivered, the subject reported a sensation of light and sustained indentation of the skin at a stimulus intensity of 1.4 μA. It was located at the same spot as the receptive field. When asked to match the size of the percept to filled circles of various size displayed on a chart the subject picked one with a diameter of 3 mm as being the nearest. He further reported that the perceptive field was oval in shape and that its long axis was oblique in relation to the finger. The quality was fairly well mimicked

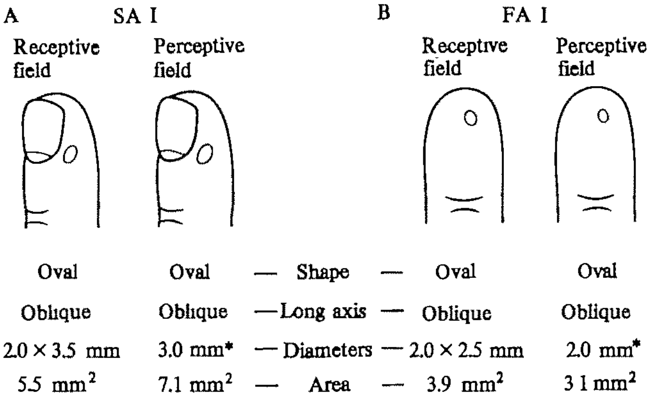


FIG. 5 Spatial properties of receptive fields of (A) an SA I and (B) an FA I unit compared with the spatial properties of percepts elicited by microstimulation through the recording electrode. * Visual matching to circular areas.

by a light and continuous pressure with compliant cellular plastic. The same procedure with the FA I unit of fig. 5B showed that the receptive and perceptive fields in this case were also of similar size and shape and that they were coincident. The stimulus rate was 25/s and the intensity 2.9 μA. The percept was described as a wobbling, fluttering sensation. For both units the sensation was judged as being almost but not quite natural. It was perceived as being not precisely on the skin surface, but slightly below and with somewhat indefinite borders.

The sample findings illustrated in fig. 5 are typical in several respects of the group data from the 59 sessions to be presented in this section although, for the two units of fig. 5, the correspondence was particularly close with regard to size, shape and orientation of the two types of fields. The material was strictly selected on the basis that the subject reported at liminal current intensity for a percept, a sensation which was located within the receptive field of the afferent unit. When spatial matching in this sense was present it was tentatively assumed that the sensation was actually based upon impulses in the recorded afferent unit being stimulated through the microelectrode. The incidence of such spatial matching was not systematically assessed; however, a rough estimate is that it occurred in about 50 per cent of the cases when a large and stable recording of a single unit was present, although there was a considerable variation between experiments in this respect. The factors involved were not explored in detail but it seemed obvious that one was the impedance of the electrode, lower impedances giving lower proportions of matching sensations.

Unit sample. The unit sample consists of 32 FA I, 3 FA II, 20 SA I and 4 SA II units. The classification was unequivocal with regard to the unit being fast or slowly adapting and also with regard to type FA I *vs* FA II. The classification of SA I *vs* SA II was more problematic in a few cases but was nevertheless imposed on the basis of the balance of evidence. Most fields were located on the volar aspects of the digits (n = 38), whereas a minority were located on the dorsal or lateral aspects of the digits (n = 17) or in the palm (n = 4). The emphasis will be on the two large groups of units, that is the FA I and SA I units, whereas the FA II and SA II units will be considered briefly in separate sections.

Electrical stimulus parameters. A rigid protocol was not followed as to the time parameters of the stimulus, but the samples of FA I and SA I units were practically identical in this respect. The current intensity required to produce a sensation in the sample of 59 selected sessions is shown in fig. 6. The median intensity was 0.81 μA (quartiles, 0.56 to 1.45 μA). Marked differences were not found between the separate unit types in this respect except that the SA II units required a stronger stimulus than other groups by a factor of 1.8 to 2.8. In quite a few cases, intensities of up to 7.0 μA were used without the subject reporting any sensation in spite of large and well isolated nerve impulses from a single unit being recorded. This was particularly evident for type SA II units.

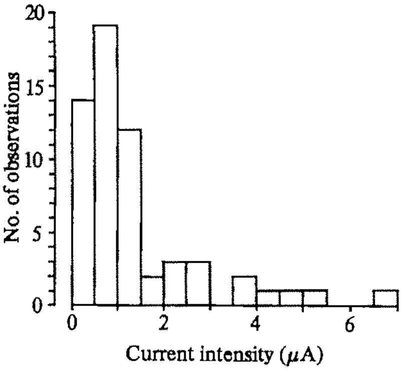


FIG. 6. Liminal current intensity required to produce a sensation located within the receptive field of the particular afferent unit which was recorded immediately before electrical stimulation through the recording electrode. Sample number = 59, median stimulus intensity = 0.81 μA.

FA I and SA I Units

Size and shape of receptive and perceptive fields. When the subjects were asked to define the size of the perceptive field, they were usually remarkably confident. Subjects often claimed that the correct size was between two neighbouring circles on the chart differing by only 1 mm in diameter (*see* Methods). In the formal treatment of the data the mean diameter of the two was used in such cases. Moreover subjects, when asked to compare the size of two perceptive fields, sometimes claimed that one was definitely larger whereas, in the later visual matching procedure, the two were found to differ by only 0.5 mm in diameter.

Fig. 7 compares the size of the receptive and the perceptive fields in mm^2 with FA I and SA I units. The quartiles of the distributions are given in the legend. It may be seen that the perceptive fields are in the same order of magnitude as the receptive fields although slightly smaller for both kinds of units. Moreover, the unit type with smaller receptive fields (FA I) was associated with smaller perceptive fields. Thus

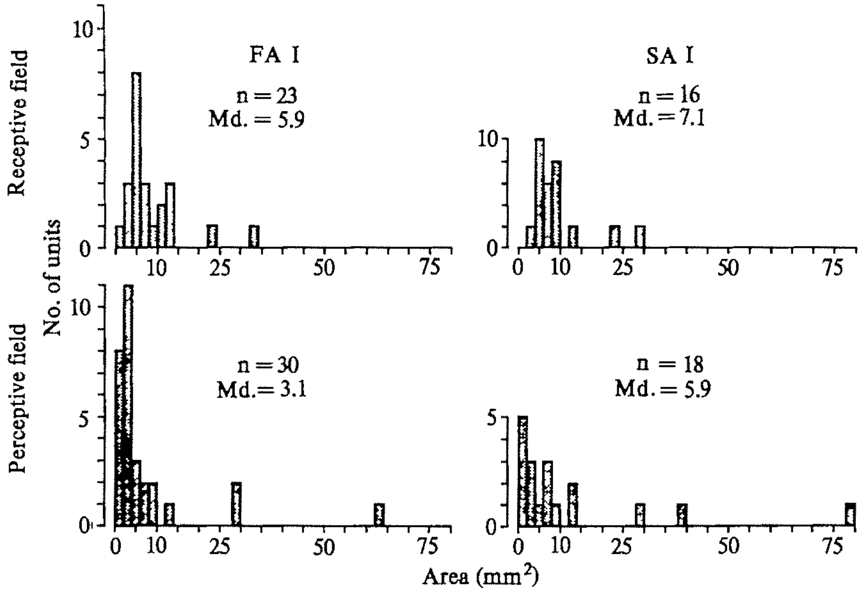


FIG. 7. Sizes of the receptive and perceptive fields of the sample of FA I and SA I units reported by the subjects on stimulation through a needle electrode with a train of electrical pulses immediately after single-unit recording. Medians are given in the diagrams Quartiles for the FA I unit data are 4.9 to 10.6 mm² and 2 1 to 6.5 mm² and for the SA I unit data 5.1 to 9.6 mm² and 2.1 to 11.6 mm²

group data indicated a close correspondence between the size of perceptive and receptive fields. Yet an analysis of the paired data from the individual units revealed only a weak positive correlation which was not statistically significant. This was partly due to a drastic mismatch for a few units, some subjects reporting a point-like sensation with some FA I units whose receptive fields were fairly large. Another factor was that the total range of field size was quite narrow so that small errors in the measurement would introduce a considerable scatter.

The examples in fig. 5 demonstrate a very close correspondence between receptive field and perceptive field not only with respect to size, but also shape and orientation. An accurate correspondence in shape was present for the majority of FA I and SA I units (22/32) for which adequate data were extracted. The contingency table of fig. 8 also demonstrates that an even larger majority of pairs of fields were, if not identical in shape, at least similar.

In most trials the sensation was evenly distributed within the perceptive field. However, stimulation of 8 out of the 27 FA I units resulted in a sensation of a number (10 to 20) of very localized indentations, somewhat like nonpainful pinpricks, within a small area. A further analysis indicated that for a high proportion of these units (6/8) the receptive field was located either on the dorsal or lateral aspects of the fingers.

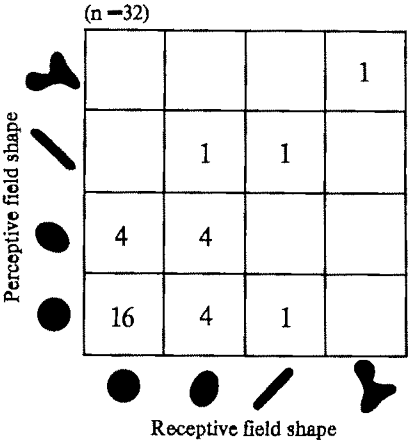


FIG. 8. Contingency table demonstrating relation between shapes of receptive and perceptive fields with 18 FA I units and 14 SA I units. The symbols represent round, oval, elongated, and irregular shapes, although an exact agreement of shape is not implied.

Further spatial attributes of percepts: borders, surface relations and stability of position. In most cases the subject reported that the borders of the perceptive field were fairly distinct although there was an obvious difference between the two unit types as shown in fig. 9A, in that the sensation with FA I units was more sharply delimited. Also when the subjects were asked to define whether the sensation was felt precisely on the skin surface or deeper, a difference was found between the two unit types, in that sensations with FA I units were more often superficially located (fig. 9B).

In all 59 cases the subjects reported that the sensation at liminal stimulus intensity was stationary and did not move from one point to another on the skin surface. However, for 6 units (3 FA I, 2 SA I and 1 SA II), there was a slight change in size of the perceptive field, the sensation spreading or shrinking during the train. Sensations of movement were, on the other hand, not uncommon when higher stimulus intensities were employed. They were often described as something moving rapidly back and forth, usually following a band along one finger.

Quality. Detailed descriptions of the qualitative attributes, in the subject's own words, would take too much space, but a few examples will be presented. The sensation elicited by stimulation of SA I units was often described as a faint and uniform pressure like that of a leaf held against the skin within a small area, but without the component of tickle which might be associated with this stimulus, or it was described as a sensation of a soft painting brush held tangentially against the skin.

The sensations elicited on stimulation of a FA I unit were often described as a wobbling or fluttering feeling which might turn into a buzzing sensation when higher stimulus rates were used, such as 200 Hz. Often the sensation of a tap was reported, particularly when the train was very short-lasting. As previously emphasized, the stimulation of some FA I units was associated with the sensation of

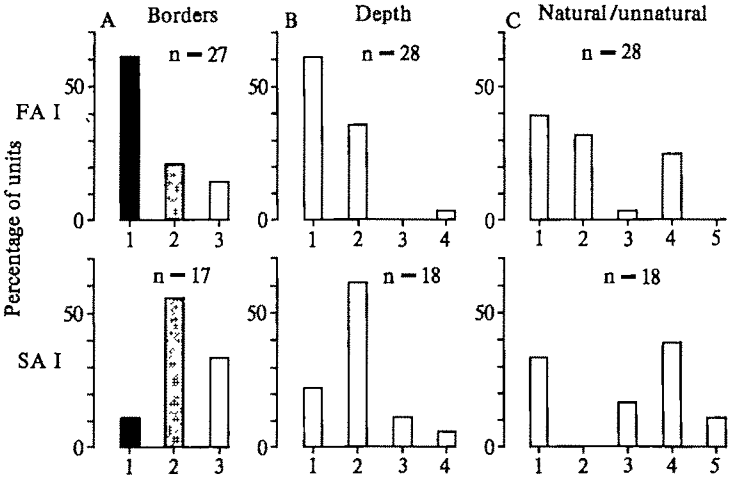


FIG. 9. Contrasting attributes of sensation with FA I and SA I units on electrical microstimulation. The three diagrams refer to separate attributes as labelled. The numbers along the abscissae indicate qualities of percepts as follows. A, Distinctness of receptive field *borders*· 1 = sharp borders; 2 = slightly diffuse borders; 3 = clearly diffuse borders B, *Depth* in relation to skin surface: 1 = precisely on the skin surface; 2 = slightly below the skin surface; 3 = clearly below the skin surface; 4 = both on the skin surface and below. C, *Natural/unnatural* sensation: 1 = completely natural; 2 = almost natural, 3 = possibly natural; 4 = rather unnatural; 5 = completely unnatural.

several points located close together being touched. One subject had an interesting comment which highlights semantic problems in studies of this nature. He reported that it was difficult to differentiate between nonsteadiness and a multiplicity of points, so that he was unsure of the best description.

The above qualitative accounts of the attributes of the percepts illustrate the general impression that the sensations, although basically of a mechanical nature, were often slightly unusual and not quite natural. When the subject was asked to rate the sensations as to whether they were natural or not the resulting judgements ranged from 'completely natural' to 'completely unnatural'. The median rank order was the one which corresponded to the judgement 'almost natural' and a significant difference was not found between FA I and SA I units ($P = 0.1$, Mann-Whitney) (fig. 9C).

When subjects were asked to describe the quality of the sensation with the aid of multiple-choice questions they reported practically only mechanical options. Fig. 10A shows the first choice with the FA I and SA I units and fig. 10B all the choices made, that is, the first as well as the second, third, etc., and that there was not an absolute difference between the two unit types. Cyclic as well as noncyclic sensations were reported for both unit types. There was a quantitative difference in that sensations of noncyclic character dominated for the SA I units, whereas cyclic and noncyclic sensations were almost equally frequent for the FA I units. Whether the sensation had a cyclic character or not was to some extent dependent on the pulse rate during train stimulation, as will be considered below. It might be significant that a sensation of continuous indentation without any cyclic components was associated with all the SA I units whose receptive and perceptive fields agreed in shape (n = 9), whereas cyclic components were reported with some SA I units whose receptive fields had a different shape than the perceptive fields.

True itching or tickle were not reported with any kind of unit but some subjects used an ambiguous term to describe the buzzing sensation often associated with high frequency stimulation of some FA I units (*see* Vallbo, 1981).

Intensity of sensation elicited by electrical train stimulation. This was assessed in 61 per cent of the cases (36/59) using a matching procedure. The subject was asked to match von Frey stimuli delivered within the receptive field with the sensation produced by the preceding electrical stimulation. He was usually quite firm in his decision as to which von Frey stimulus was most adequate. Electrical train stimuli with pulse rates of 20 to 100 Hz produced sensations corresponding to von Frey stimuli with a median of 8 mN (quartiles, 4 to 16 mN) with no major difference between the two unit types. On the other hand, only 1 to 3 impulses were usually elicited from the afferent unit (n = 13) when mechanical stimuli of matching intensity were delivered, suggesting that intensity is normally coded partly by the number of units recruited. It should be pointed out that the sensations were well above threshold intensity for psychophysical detection which usually was 0.5 to 2 mN. Thus most sensations, although weak, were clearly strong enough to be easily and immediately noticed by the subjects.

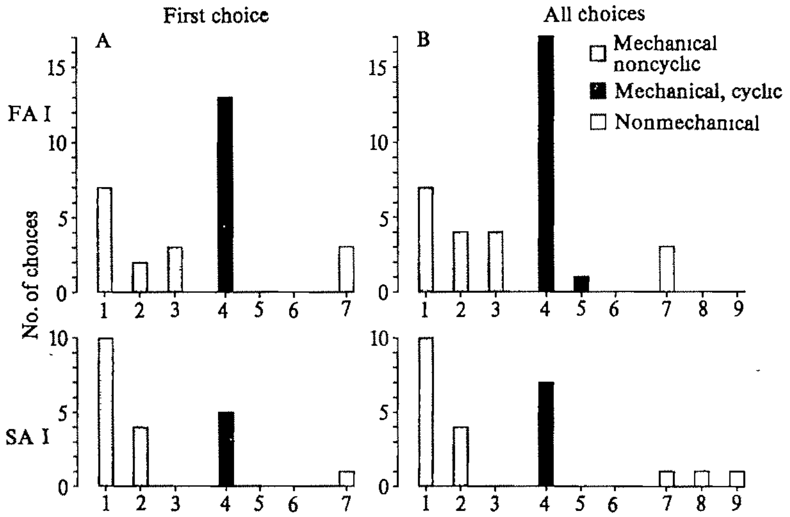


FIG. 10. Quality of sensation induced by electrical microstimulation of FA I and SA I units. The subjects' *first choice* on confrontation with the multiple choice question is presented in left-hand diagrams (A) and *all choices* in the right-hand diagrams (B). The separate qualities are indicated by code numbers along the abscissae 1 to 3 represent noncyclic mechanical sensations and 4 to 6 cyclic mechanical sensations. 1 and 4 = indentation; 2 and 5 = pull or pinch; 3 and 6 = prick; 7 = nonspecified mechanical sensation; 8 = warmth; 9 = sensation of electric current.

Effect on attributes of sensations of pulse train parameters. Lower pulse rates were more often associated with a cyclic sensation than higher rates, as was evident from pooled data. The effects were also studied in 8 individual FA I units stimulated at two or more rates between 25 and 100 Hz. With all but one unit the quality was not altered from one category to another (*see* Methods). In one case the subject reported that stimulation at 100 Hz gave the sensation of a tap, that is, a noncyclic sensation, but at 25 Hz gave the sensation of flutter-vibration. Intensity of sensation was not explored, nor pitch of flutter-vibration, as a function of pulse rate.

The minimal pulse rate and number of pulses for detection were studied with 8 units (fig. 11). One stimulus pulse was sufficient for detection with 4 out of 6 FA I units. For the other 2 FA I units, 3 to 5 and 6 to 12 pulses, respectively, were required; the exact number was not assessed. The latter pair of figures refer to a unit with a receptive field on the dorsal aspect of the index finger. With 2 SA I units no sensation was reported when 10 pulses at the rate of 20 Hz were used, but a noncyclic sensation was experienced when 20 pulses at 40 Hz were delivered.

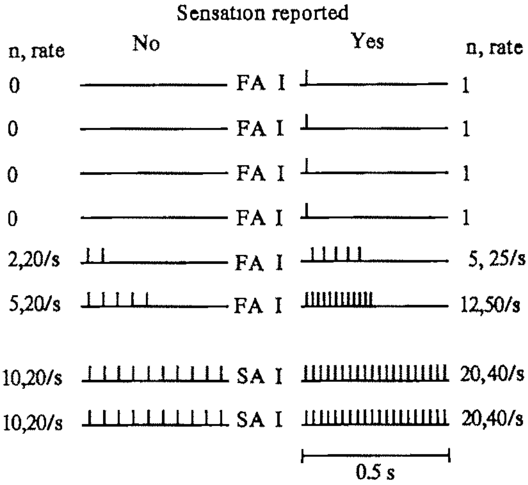


FIG. 11. Liminal train parameters for eliciting a sensation on microstimulation with 8 separate units of the types indicated. The receptive fields were located on the volar aspect of the fingers except for the last FA I unit in the column whose field was located on the dorsal aspect of the index.

FA II and SA II units. Because the samples of FA II and SA II units were small (n = 3, n = 4) they will not be described in detail. Qualitative statements based upon the median of the possible choices will be presented. The 3 FA II units were all located on the volar aspect of the fingers and they were stimulated at 100 Hz. Attributes of the sensations showed considerable but not absolute similarity. All 3 subjects reported a sensation of vibration, which extended over a continuous and fairly large area (28.3 mm^2) with diffuse borders. The sensation was localized slightly below the skin surface and it was judged to be almost natural.

The 4 SA II units were also located on the volar aspects of the fingers. In contrast to the FA II units, attributes of the sensations were strikingly nonuniform in several respects. The quality of the percepts ranged from sustained lateral pulling of the skin to a sensation of flutter. They were judged to range from completely unnatural to almost natural. On the other hand, there was considerable uniformity in other respects. The extent of the sensations on the skin surface was large for all 4 units (35.8 mm^2), the sensations were located deeply or slightly below the skin surface, and the borders of the perceptive fields were diffuse.

DISCUSSION

The Activation of Identified Single Afferents

The present report provides evidence that it is possible to activate identified unitary afferents by electrical stimulation through a needle electrode inserted in the nerve and, moreover, that such activation may give rise to a distinct and well-localized sensation of mechanical deformation when a tactile unit is stimulated. Most convincing evidence for these conclusions was obtained when the spatial attributes of the receptive field of the afferent unit agreed in detail with spatial attributes of the percept. This was found for several units not only with respect to the size and shape of the fields but also their orientation when the field was noncircular. In addition, a number of other findings provided subsidiary support. One was that an increase of the stimulus above liminal intensity resulted in quantal changes in perceptive experience. At definite levels of intensities additional percepts of mechanical deformation appeared. They were located at semirandom distances from the first percept which, on the other hand, remained invariant. This very regular finding would be most feasibly explained by assuming that additional single afferents were successively excited and accounted for the additional separate sensations. Moreover, the dependence between, on the one hand, unit type, and on the other, a number of attributes of the percepts as found in group data, strongly suggests a link between the recorded afferent and the percept, even though this dependence was not always present with the individual unit.

It should be emphasized that the pairs of unit-percept data presented were selected solely on the basis of a coincidence of receptive and perceptive fields. Any other observation, such as field shape or quality of the sensation, was not allowed to influence the sample selection, however strongly such an observation suggested that another unit with the same receptive field location accounted for the sensation. The purpose was to avoid circular argument with regard to the differential effect of the afferents and the association between receptor type and percept. Clearly the possibility exists that another unit with an identical receptive field location occasionally accounted for the sensation. Nor can it be excluded that more than one unit was occasionally stimulated when only one percept was reported. The probability of such double stimulation would be low, however, considering the evidence found in the present study for a semirandom distribution within the nerve fascicle at the level of exploration (above the elbow) in relation to the location of their perceptive fields (figs. 3, 4). Neither does the experimental strategy preclude the possibility that an extra afferent unit was occasionally excited which did not contribute to the percept. The existence of units which are perceptually mute with certain train parameters was suggested by the observation that strong current stimulation sometimes was not effective in eliciting a sensation in spite of a large unit being recorded immediately before. This was particularly often seen with units of the SA II type. Moreover, direct tests clearly demonstrated that units varied with regard to their power to induce a percept. For some units one impulse was sufficient, whereas for others a substantial number were required to produce a sensation.

On the other hand, there is no doubt that the present technique allows the selective activation of single nerve fibres which can also be recorded through the same electrode. It was demonstrated in separate control experiments on exposed nerves that stimulation through the needle electrode may produce such activation using a current intensity of the magnitude employed in the present study. The relatively coarse tip of the electrode apparently impales the fibre and presumably causes some deterioration in excitability (Vallbo, 1976), which might account for the larger current intensity compared with stimulation of intact unitary fibres through a micropipette (Roberts and Smith, 1973).

Attributes of Percepts on Single Unit Activation.

The sensations were located within a small area, typically 3 to 6 mm^2, with the FA I and SA I units. Their receptive fields are only slightly larger. In this context it is interesting that the end organs of these two types of units are located within an area which is slightly smaller than the receptive field as defined by the method used in this study (Johansson, 1978). With the group of SA I units the two kinds of fields were larger than those of the FA I units. The correspondence in shape between the two kinds of fields was also striking (fig. 8). Thus group data on field size as well as field shape suggest that the extent of the percepts match reasonably well the area over which the end organs are distributed, suggesting that the spatial properties of the percept are constructed with an amazing accuracy on the basis of an input probably not previously encountered by the brain.

There were clear differences in the group data between FA I and SA I units with regard to the attributes of the associated sensations, although absolute differences were not found with the present strategy of analysis. The percepts with SA I units were characterized by more diffuse borders and the sensations were referred to a slightly deeper layer below the skin surface. Whether it is significant or purely coincidental that the receptive fields of the SA I units have more diffuse borders (Johansson, 1978) and that their end organs are more deeply located (Miller *et al.*, 1958), is of course impossible to state. With respect to quality, about 50 per cent of the FA I units were associated with a sensation of flutter-vibration, whereas the majority of the SA I units were associated with a noncyclic deformation. A difference of this nature is to be expected on the basis of the analyses of Mountcastle and his coworkers (Talbot *et al.*, 1968; Mountcastle *et al.*, 1969). At first sight it might appear surprising that almost 50 per cent of the FA I units were associated with noncyclic sensations, that is, there was no element of flutter or vibration. However, it seems feasible that the sensation of flutter is dependent not only on the mere firing of FA I units, but also on the properties of the impulse discharge, such as rate and duration. An effect of rate was demonstrated in the present study. With natural stimulation a short-lasting burst of impulses from FA I units may be produced by a variety of mechanical stimuli, such as a localized indentation, a withdrawal of an indentation, or a short-lasting vibratory stimulus, as well as an indentation moving along the skin surface. Moreover, a difference in perceptive effects between individual FA I units may be related to a well-known difference in receptive properties of their sense organs (Talbot *et al.*, 1968; Knibestöl, 1973). Some of the FA I units fire only in response to very rapid changes when stimulated mechanically. A continuous discharge for any length of time is therefore normally only produced by a cyclic stimulus in these units. Admittedly a stimulus moving over the surface might also produce a continuous discharge, but then the set of active units would be continuously shifting, providing an altogether different spatio-temporal impulse pattern. Other FA I units may respond with a more long-lasting and continuous discharge during a slowly rising indentation. The impulse trains of these units, alone or in combination with other inputs, is probably interpreted by the brain as a noncyclic indentation. Thus it is reasonable to assume that two groups of FA I units exist—or they may be two extremes in a continuum. One has a high critical slope on mechanical stimulation and elicits a sense of flutter-vibration when a period of regular discharge exceeds a critical time; the other has a low critical slope. A similar discharge in these afferents would elicit a sense of noncyclic indentation. Further analysis is obviously needed to confirm this hypothesis, which suggests an intimate relationship between detailed receptive properties of the afferent and its perceptive effects within the mind.

The fact that a sizeable minority of the SA I units were associated with cyclic sensations seems more puzzling. This may indicate that an FA I unit with an identical receptive field location was stimulated and accounted for this sensation, considering that the FA I units constitute the largest group and also are more powerful in eliciting a sensation. This interpretation is consistent with the fact that the shape of SA I receptive fields was often different from the perceptive fields when cyclic sensations were reported. Some FA I units gave rise to a sensation of several points rather than of a continuous area being indented. Most of these units were located on the lateral or dorsal aspects of the fingers. This finding suggests either that a separate kind of FA I unit exists which is present mainly in the nonglabrous skin or that the relevant brain mechanisms handle the information differently from the glabrous and nonglabrous skin in the production of percepts on the basis of impulses in FA I units. A difference between separate skin regions of the hand with regard to central processing involved in perception has previously been shown in detection experiments (Johansson and Vallbo, 1979*a*).

The quality associated with the small group of FA II units suggests that a single pacinian corpuscle unit may produce a sensation of vibration at the stimulus rates employed. Considering the wealth of previous work on this system (Talbot *et al.*, 1968; Mountcastle *et al.*, 1969), a vibratory quality is certainly the most reasonable one to expect from these units. On the other hand, the fact that a single FA II afferent is effective contradicts the claim that the pacinian system involves summation. On the basis of psychophysical studies, Verrillo (1963, 1968) concluded that several afferents in this system must be activated to produce a vibrotactile sensation. The discrepancy may be resolved if it is assumed that there are regional differences within the hand, as demonstrated for other psychophysical functions (Johansson and Vallbo, 1979*a*). Thus FA II afferents from the fingers may have a more powerful access to the perceptive levels of the somatosensory system than afferents from the thenar region tested by Verrillo.

We suspect that the sensations reported when attempts were made to stimulate SA II units were often the result of activation of other units. This interpretation is mainly based on the finding that a large group of SA II units were recorded which on stimulation, even at high intensities, failed to elicit any sensation, and which were therefore not included in the sample.

The present report provides direct evidence that units characterized by different receptive properties also produce qualitatively different sensory effects. The findings thus support the psychological aspect of the general theory of specificity in sensory systems, even within the tactile submodality of the somatosensory system. The findings directly refute one of the basic predictions of the pattern theory which is the main alternative (Melzack and Wall, 1962; Wall, 1971). The pattern theory predicts that more than one afferent fibre must be excited for the qualitative characteristics of a sensory stimulus to be defined perceptually (Melzack and Wall, 1962). In the present study, subjects clearly reported sensations of a tactile nature when a single afferent fibre was stimulated. Moreover, the quality even varied with different tactile afferents.

Central Mechanisms

It has previously been pointed out that the FA I and SA I units in the hand probably constitute the peripheral organization responsible for our capacity to discriminate tactile stimuli spatially and to recognize surface structures. This interpretation is now supported by three sets of independent findings which are of a fundamentally different nature. The receptive fields of the afferent units are small and well defined (Johansson, 1978), which implies that they constitute a fine grain system capable of extracting accurate information concerning spatial features. Further, the density of these units varies between different skin regions and this variation parallels the discriminative capacity as studied in psychophysical tests with a reasonable degree of accuracy (Vallbo and Johansson, 1978; Johansson and Vallbo, 1979*b*). Finally, it was shown in the present study that activity of the individual afferent fibres produces a well-localized sensation in conscious experience, indicating that the high resolution is also preserved at this level.

The finding that a single impulse in a single FA I unit may be detected psychophysically confirms an earlier report when natural stimuli were employed (Johansson and Vallbo, 1979*a*), whereas it was also shown that a series of impulses in a single SA I unit does not produce a percept unless the rate is reasonably high. This suggests that the normal sensation of a light sustained skin indentation requires the joint effect of several afferents discharging at low rates. Thus the FA I units are characterized not only by a higher sensitivity to mechanical deformation compared with SA I units (Johansson and Vallbo, 1979*a*) but also more powerful connections to the perceptive levels of the somatosensory system.

It is of interest to compare the present data with findings obtained with liminal stimulation of the somatosensory cortex in conscious man (Libet, 1973, 1982; Libet *et al.*, 1975). Unfortunately the percepts which are elicited by threshold stimulation of the cortex are not described very accurately and a detailed comparison is therefore not possible. Nevertheless, it is obvious that there are drastic differences in comparison with the present findings. Paraesthetic sensations are common with liminal stimulation of the cortex but they do not occur with afferent stimulation at threshold intensity; this always gives rise to a sensation of a mechanical event within a small area of the skin surface. Moreover, only a small minority of the nonparaesthetic or 'natural-like' percepts on cortical stimulation are of surface 'mechano-type' or vibration (9 per cent) (Libet, 1973, 1982; Libet *et al.*, 1975). Many of these, in turn, are complex and include a prominent element of movement, such as 'rolling (a ball, etc.) over surface; water running over surface; . . . rubbing something between thumb and index finger'. Stimulation of afferents, on the other hand, always produces a sensation of a stationary and localized deformation providing liminal intensity is not exceeded. To what extent the 'natural-like' sensations were natural in a similar sense as the term was used in the present study seems impossible to assess, but some of the descriptions reported resemble those occasionally produced in the present study at supraliminal intensities, such as 'something running back and forth along a band' which our subjects characterized as nonnatural. There is no clear statement about the extent of the percepts on cortical stimulation but the impression emerging from the reports is that they are larger than 2 to 3 mm^2. For instance 'rolling (a ball, etc.) over surface' or 'rubbing something between thumb and index finger' would apply to a larger area. Moreover, there is no explicit statement of the perceptive field being confined to a small area whereas, in fact the experience of a small and well-localized, but still not point-like, deformation is quite striking as was spontaneously emphasized by several subjects.

Sensations of mechanical deformation of the skin evoked by cortical stimulation are thus infrequent and apparently more complex, less natural, and extend over larger areas than the percepts reported in the present study. These differences indicate that different sets of nerve cells are activated at the perceptual level of the brain to produce the sensations. If activity in a small group of neighbouring cells in the somatosensory cortex, for example the cells of a cortical column, would constitute the basis of the percepts associated with single afferent stimulation, it would be expected that such percepts would occur in a proportion of cases on cortical stimulation. Since similar sensations do not seem to occur it is reasonable to suggest that the reproduction in perceptive dimensions of the receptive field of a single afferent is dependent on distributed activity within a larger cortical area or even within several brain regions which are simultaneously activated. In this context it is interesting that the receptive fields of cortical cells within the hand region of the somatosensory cortex in the monkey are comparatively large and often cover a whole phalanx (Horne and Tracey, 1979; Sur *et al.*, 1980). If this cortical region or any organization of neurons with similarly large receptive fields extracts the spatial attributes of the sensations associated with peripheral microstimulation, it follows that quite an accurate overlap region, common for a large group of cortical receptive fields, must be constructed on the basis of the faint and exotic input of the single afferent, whatever form such a construct may take.

Note Added during Course of Publication

Since this manuscript was submitted a series of papers have appeared which are based on essentially the same method and focus on similar problems (Ochoa J L, Torebjörk H E (1983) Sensations evoked by intraneural microstimulation of single mechanoreceptor units innervating the human hand. *Journal of Physiology, London*, **342,** 633-654; Schady W (1983) Projections of sensory fibres in the human median nerve. Abstract. Dissertation, Faculty of Medicine, University of Uppsala; Schady W, Ochoa J L, Torebjörk H E, Chen L (1983) Peripheral projections of fascicles in the human median nerve. *Brain*, **106,** 745-760). The findings and the conclusions seem to agree on most points when corresponding data are available.

ACKNOWLEDGEMENT

This study was supported by grants from the Swedish Medical Research Council (Project No. 3548), and by Gunvor and Josef Aners Stiftelse.

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(*Received June 28, 1983. Revised December 6, 1983*)

Brain (1984), **107**, 751-758

FACIAL SWEATING IN HORNER'S SYNDROME

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SUMMARY

The distribution of sweating on the face was studied in 31 patients with Horner's syndrome. In patients whose lesion was known to be distal to the bifurcation of the common carotid artery impairment of sweating was confined to the medial aspect of the forehead and side of the nose. In more proximal lesions loss of sweating involved the whole of one side of the face. Facial sweating was normal in 6 patients with avulsion injuries of the brachial plexus and in 2 patients with a lateral medullary syndrome. These findings suggest that the pattern of sweating in Horner's syndrome may be useful in some patients in localizing the site of the lesion.

INTRODUCTION

The syndrome described by Horner (1869) comprises partial ptosis, miosis with normal pupillary constriction in response to light, and loss of sweating on the face. Other features which may be present include elevation of the lower lid, loss of the ciliospinal reflex, heterochromia iridis and loss of the lid fold (Walsh and Hoyt, 1969). Facial flushing and ocular hypotony may occur transiently. The anisocoria of Horner's syndrome is more marked after 5 s in dim light than after 15 s. This dilatation 'lag' is not seen in simple anisocoria (Thompson *et al.*, 1982). The presence of these signs signifies a lesion of the sympathetic pathway (Pourfour du Petit, 1727; Bernard, 1852). Such is the length and complexity of this pathway that Horner's syndrome, as an isolated finding, is of little value in localizing the site of the lesion. Pharmacological tests have been used to determine whether the lesion is proximal or distal to the superior cervical ganglion (Thompson and Mensher, 1971). The ciliospinal reflex may be helpful in distinguishing peripheral from central lesions (Reeves and Posner, 1969). The purpose of this study was to determine whether the pattern of sweating on the face is also of value in localizing the site of the lesion.

METHODS

Over a three-year period all patients referred to the Westmead Neurology Department with a diagnosis of Horner's syndrome were studied. Most were inpatients. The diagnosis of Horner's syndrome was based on the findings of unilateral partial ptosis and miosis with normal pupillary response to light. In all cases anisocoria was observed to increase in dim light. Cocaine eye drops (5 per cent) were used to confirm the diagnosis in some patients. A full neurological and ophthalmological assessment was made and a number of baseline investigations performed. These included a full blood picture, ESR, random blood sugar, syphilis serology and chest x-ray. Skull x-rays, CT scans of the head and cerebral angiography were undertaken where indicated. Alizarin powder, a yellow dye similar to Quinizarin (Guttmann, 1941) which becomes purple when wet, was applied to the face using a cotton wool ball. The patient was then heated with warm air in the manner described by Bajada *et al.* (1980). Heating was continued until sweating had occurred on the forehead and around the mouth on the normal side of the face. This usually took 20 to 30 min. The distribution of sweating was recorded by a drawing, supplemented in most cases by a photograph.

RESULTS

Thirty-one patients fulfilled the criteria for entry into the study. The results are summarized in the Table. Patients were divided into four groups on the basis of their facial sweating.

Group 1. Hemifacial Anhidrosis

In 12 patients little or no sweating occurred on the side of the face with the Horner's syndrome. The site of the lesion was known in 10 of these patients from associated signs or from the circumstances which had resulted in the Horner's syndrome. In all 10 the lesion was proximal to the bifurcation of the common carotid artery.

Group 2. Selective Anhidrosis

Loss of sweating in the 6 patients in this group was apparent on the medial aspect of the forehead (*see* fig. 1). In 4 of these patients the side of the nose also failed to sweat (in the remainder sweating did not occur on either side of the nose). Two presented with headache and were found to have aneurysms of the internal carotid artery immediately proximal to its entry into the carotid canal. Case 2 presented with pain and numbness in the distribution of the ophthalmic division of the trigeminal nerve. A clinical diagnosis of Raeder's syndrome was made. The patient declined angiography. Case 16 had cluster headaches. Horner's syndrome associated with cluster headache and Raeder's syndrome is thought to be due to a lesion distal to the superior cervical ganglion (Grimson and Thompson, 1980). Also included in this group is Case 1 whose Horner's syndrome was the result of perineural spread from a basal cell carcinoma on the side of his nose into branches of the first and second divisions of the trigeminal nerve. Loss of sweating included the upper lip but it was felt that this resulted from the biopsy of the infraorbital nerve by which the diagnosis was made. Sweating on the lower lip, chin and outer aspect of the forehead was normal. In this case the sympathetic fibres were involved at the level of the nasociliary nerve. Further details are published elsewhere (Morris and Joffe, 1983).

In this group of patients the lesion was known to be distal to the bifurcation of the common carotid artery in 3 (Cases 1, 9, 12) and was likely to be distal to the bifurcation in a further 2 (2, 16). In 1 patient the site of the lesion was unknown.

TABLE. PATTERN OF SWEATING LOSS IN PATIENTS WITH HORNER'S SYNDROME

Patient				
No.	*Age (yrs)*	*Sex*	*Other signs*	*Diagnosis/site of lesion*
Group 1. Hemifacial anhidrosis				
3	48	F	Ipsilateral V, VII (LMN) and gaze palsy; contralateral hemianaesthesia	Pontine infarct
4	53	F	Heterochromia iridis	Congenital Horner's syndrome
6	23	F	None	Ganglioneuroma of the stellate ganglion
7	69	F	Ipsilateral weakness and sensory loss in a C8–T1 distribution	Pancoast tumour
10	30	F	None	Post-thyroidectomy
15	52	F	Paraparesis with ipsilateral sensory level at T2	Pancoast tumour
21	37	M	None	Post-thoracic surgery
24	67	F	Ipsilateral VII (LMN). Ataxia of gait	Pontine infarct
26	56	F	Ipsilateral weakness of C8, T1 muscles and sensory loss in C8–T2 distribution	Pancoast tumour
27	54	M	None	Malignant pleural effusion
29	62	M	Ipsilateral weakness and sensory loss in a T1 distribution	Neurilemmoma at lung apex
30	30	F	None	Followed Cloward's procedure at the C6–7 level
Group 2. Selective anhidrosis				
1	67	M	Ipsilateral numbness in V_1 and V_2, weakness in distribution of buccal branch of VII	Perineural spread from skin, basal cell carcinoma
2	56	M	Ipsilateral sensory loss in V_1	Raeder's syndrome
9	52	M	None	Extracranial aneurysm of internal carotid artery
12	47	M	None	Extracranial aneurysm of internal carotid artery
16	42	M	None	Cluster headache
20	65	M	Contralateral VII (UMN)	Unknown
Group 3. No anhidrosis				
5	20	F	None	Acute onset during diabetic ketoacidosis. Site unknown
8	30	M	Ipsilateral paralysis and sensory loss in a C7–T1 distribution	Avulsion injury of brachial plexus
13	25	M	Ipsilateral paralysis and sensory loss in a C5–T1 distribution	Avulsion injury of brachial plexus
14	40	M	Ipsilateral V (pain and temperature) and ataxia; contralateral hemianaesthesia	Lateral medullary infarct
17	18	M	Ipsilateral paralysis and sensory loss in a C5–T1 distribution	Avulsion injury of brachial plexus
19	52	F	Ipsilateral V (pain and temperature) and ataxia; contralateral hemianaesthesia	Lateral medullary infarct
25	22	M	Ipsilateral paralysis and numbness in a C5–T1 distribution	Avulsion injury of the brachial plexus
28	19	M	Ipsilateral paralysis and numbness in a C5–T1 distribution	Avulsion injury of the brachial plexus
31	37	M	Ipsilateral paralysis and numbness in a C5–T1 distribution	Avulsion injury of the brachial plexus
Group 4. Partial anhidrosis (slight asymmetry)				
11	69	F	Contralateral hemiparesis	Site unknown
18	25	M	Contralateral hemianaesthesia	Site unknown
22	26	M	Contralateral hemianaesthesia	Thalamic glioma
23	46	F	None	Site unknown

Group 3. No Anhidrosis

The 9 patients in this group sweated symmetrically on the two sides of the face. In 6, Horner's syndrome resulted from avulsion of the roots of the brachial plexus, usually from a motor-cycle accident. In all cases avulsion was confirmed by myelography and nerve conduction studies. Two patients had the signs of a lateral medullary infarct. The site of the lesion was unknown in 1 patient (Case 5).

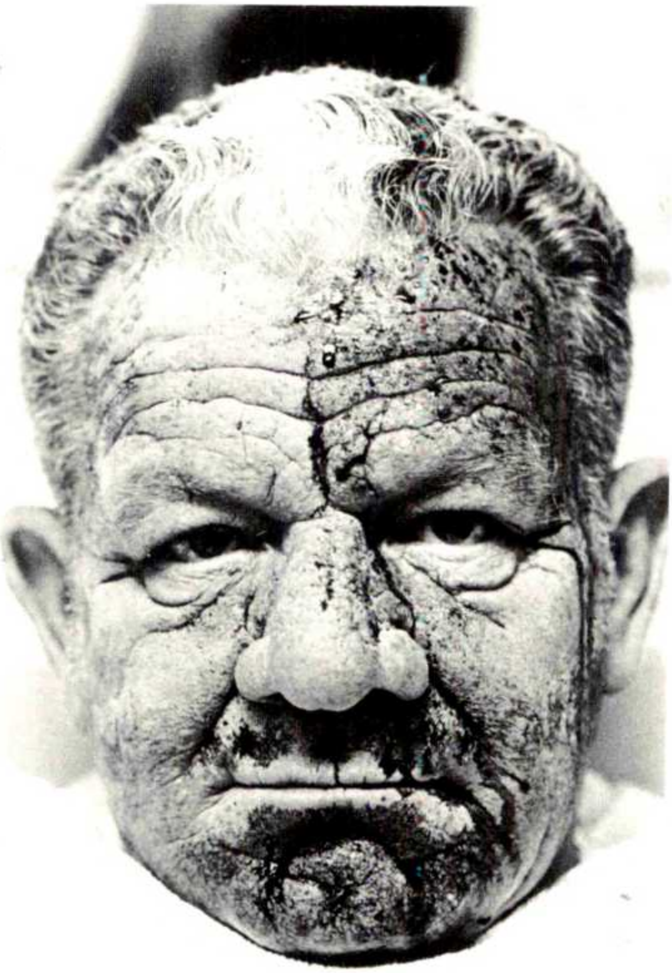

FIG. 1. The distribution of sweating in *Case 2*.

Group 4. Slight Asymmetry

Patients in this group sweated slightly less generally on the side of the Horner's syndrome. Ptosis and miosis were usually less marked than in patients in the other groups. Case 22 posed a particular problem as he had a luxuriant beard with which he was loath to part but which precluded a study of sweating in the lower face.

The site of the lesion and pattern of sweating in the 23 patients in whom the lesion was known are shown in fig. 2.

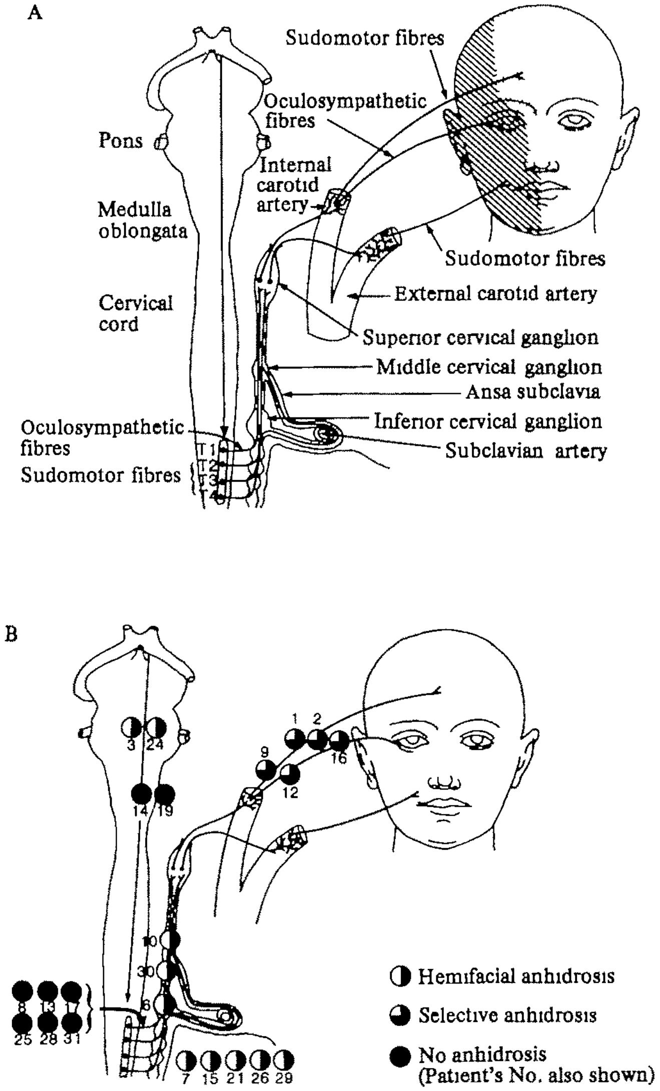

FIG. 2. A, sympathetic pathway to the face (adapted from *Cunningham's Textbook of Anatomy*, by permission of Oxford University Press). B, site of the lesion and pattern of facial sweating in 23 patients.

DISCUSSION

It is commonly stated (Keane, 1979; Jaffe, 1950; Giles and Henderson, 1958) that facial anhidrosis does not occur when Horner's syndrome results from a lesion of the postganglionic fibres. This is said to be due to the fact that while sympathetic fibres to the eye travel with the internal carotid artery after leaving the superior cervical ganglion, those destined for the sweat glands on the face accompany the external carotid artery. In a study of 12 cases of Horner's syndrome due to internal carotid thrombosis, O'Doherty and Green (1958) observed facial anhidrosis in only 1 patient and in his case the external carotid artery was also thrombosed. It is not stated, however, how facial sweating was assessed in these patients. Of 9 patients with Raeder's syndrome examined by Boniuk and Schlezinger (1962), 7 sweated normally. In 2 patients anhidrosis was confined to the forehead. Again no mention is made of how sweating was assessed. In a careful study of facial sweating using Minor's iodine and starch method, List and Peet (1938) described a patient with 'a syndrome of the right internal carotid plexus'. From the history given it seems likely that he had cluster headaches. Loss of sweating in this patient, as in our Group 2 patients, was confined to the distribution of the ophthalmic division of the trigeminal nerve. This observation led the authors to conclude that the sympathetic fibres for the sweat glands of the forehead run with the internal carotid artery from which the blood supply of the forehead also arises (Romanes, 1964). They went on to show that the sweat fibres leave the internal and external carotid arteries to join terminal branches of the trigeminal nerve before they reach the skin on the face. It is possible that the incidence of selective loss of sweating as seen in the patients in Group 2 has been underestimated in the past. In response to a heat stimulus, sweating is most obvious on the upper lip and forehead. It would be easy to miss the small area of anhidrosis over the medial aspect of the forehead and over the side of the nose if the areas of normal sweating were not clearly defined using alizarin or other agents. Our findings suggest that when this abnormality of sweating occurs it is likely to be due to a lesion of the postganglionic sympathetic fibres.

A surprising observation was that none of the 6 patients with avulsion injuries of the roots of the branchial plexus had an abnormality of sweating. By contrast 5 patients with lesions of the lung apex had hemifacial anhidrosis. The site of the lesion in both groups was presumably similar. An explanation for this disparity is provided by the observations of Goetz (1948). Using the techniques of stimulation and ablation of the exposed lower cervical and upper thoracic roots he was able to show that most of the pupillary fibres leave the spinal cord in the T1 ventral root. Fibres destined for the sweat glands of the face leave the spinal cord mainly in the T2 to T4 ventral roots. Hyperhidrosis of the face could be abolished in 90 per cent of patients without producing ptosis or miosis by resecting the T2 to T4 sympathetic ganglia. That sweating was spared in the patients with avulsion injuries was thus probably due to the fact that the thoracic roots below T1 were not involved. In Pancoast tumour, Horner's syndrome results from invasion of the inferior cervical ganglion. This lies in close proximity to the apex of the lung and receives sympathetic fibres from the upper four thoracic roots (Warwick and Williams, 1975).

Central lesions accounted for only 5 of the cases in this series: 2 had hemifacial anhidrosis, 2 sweated normally and 1 had slightly reduced sweating on the affected side. When anhidrosis is due to a central lesion it often involves the whole of one side of the body (Carmel, 1968).

Pharmacological tests using phenylephrine and hydroxyamphetamine eye drops are widely used to determine whether the lesion in Horner's syndrome is pre- or postganglionic. While providing valuable information in many patients, a number of problems limit their use in practice: (1) the response of a dark iris to dilating drugs is often poor; (2) it is difficult to ensure that the same amount of drug is absorbed by each eye, this factor being of particular importance when testing for denervation hypersensitivity (Thompson and Mensher, 1971); (3) there is a theoretical risk that pupillary dilatation may precipitate angle closure glaucoma in susceptible patients.

In conclusion, the study of facial sweating involves simple inexpensive apparatus, causes little discomfort to the patient and yields useful information on the site of the lesion in Horner's syndrome. It is of most value when anhidrosis is clearly seen in half the face, or selectively involves the medial aspect of the forehead and half the nose. Normal sweating or slight asymmetry of sweating are findings of no localizing value. In the majority of patients with Horner's syndrome, localization of the site of the lesion is made possible by the presence of other signs and by the circumstances which led to the lesion. This test is recommended in patients where the site of the lesion is unknown.

ACKNOWLEDGEMENTS

We wish to acknowledge Dr M. B. Kappagoda's role in initiating this study and to thank Professor J. G. McLeod for his helpful advice and criticism in the preparation of the manuscript.

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(*Received November 8, 1983*)

Brain (1984), **107**, 759-785

HYPERLEXIC CHILDREN READING

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SUMMARY

Eight hyperlexic children participated in the study. All had language delays, displayed difficulties in integrated behaviour and interpersonal relationships, and learned to read with little or no formal instruction (usually before the age of 5 years). Tests assessing cognitive and academic functioning were administered. In general, nonverbal skills were stronger than verbal skills. Reading ability was in the grade 4 to grade 6 range as based upon Peabody Individual Achievement Test (PIAT) Reading Recognition scores. A wide variety of tests assessing phonological and lexical reading routes, as well as metalinguistic processing, were also administered.

It appeared that the hyperlexic children were able to reach the lexicon *via* both the visual-orthographic and phonological pathways. Error analysis indicated the former was preferred. Hyperlexic children had an organized, though limited, lexicon. Imagery had a significant effect on their reading. Further, they were able to comprehend single words and sentences, but not paragraphs. As only 3 of the 8 children seemed to have metalinguistic awareness, it becomes problematic whether the 'cognitive unconscious' is necessary for reading. Also, while the hyperlexic children might have acute visual registration mechanisms for written language, they have abstracted grapheme-phoneme transformation rules as indicated by their ability to read pseudowords.

INTRODUCTION

Hyperlexia has been alluded to anecdotally in studies of autistic children by Kanner (1947) and in the savant literature. The term was introduced by Silberberg and Silberberg (1968-69) who used it to refer to children who recognized words mechanically at a higher instructional level than was indicated by their intellectual potential. The definition is patently overinclusive. Different criteria have been proposed by Huttenlocher and Huttenlocher (1973), Mehegan and Dreifuss (1972), Cobrinik (1974), Elliott and Needleman (1976), and Healy *et al.* (1982). In this paper, hyperlexia will be used to refer to an isolated ability to read words aloud which is manifested prior to formal instruction and set against generalized language arrest and/or behavioural fragmentation.

Based upon a data bank of 5,400 autistic children, parents of 531, using a questionnaire format, believed that their children displayed savant skills (Rimland, 1978). For 119, detailed information existed. Nineteen of the 119 were considered to have pseudoverbal skills, including hyperlexia. Rimland believed that classical autistic children were genetically endowed with a predisposition towards high intelligence and thus displayed a much higher prevalence of savant skills. The male:female ratio in hyperlexia is between 5:1 and 10:1, the ratio in autistic children in general being 4:1.

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Scheerer *et al.* (1945) studied an 11-year-old boy who was hyperkinetic, manifested finger stereotypies, and was self-preoccupied. He was usually restless or self-absorbed and aloof, although he displayed a mechanical politeness when responding to others. By his fifth year he had learned the letters of the alphabet from toy blocks and could spell out words. The process by which he was able to do this was not noted. 'His ear for sounds was good so that after "go" was spelled for him he could spell "so" and "low" [*sic*].' Conversation was then at a primitive stage; speech was dysarthric and language was often irrelevant and filled with jargon. Scheerer *et al.* believed that hyperlexic children and, more broadly, idiot savants have difficulty grasping abstract concepts and the symbolic meaning of language. An impairment of the abstract attitude thus results in an inability to use language in a symbolic sense, to grasp its properties in the abstract, and to comprehend similarities or differences. An inflexible style in which performance cannot be lifted out of its concrete context for reflection then becomes manifest.

Cain (1969) reported in detail 3 cases of hyperlexia in childhood psychosis. A 6.5-year-old girl whose functioning was marked by aimless roaming, staring, and muteness read and reproduced any word she had ever seen. She also could write backwards as well as forwards. These activities occurred only spontaneously and not upon request. The second, a 7-year-old girl, was preoccupied, 'unseeing and unhearing and not in contact'. Speech was perseverative although communicative. This girl read single words before the age of 2 years, and at 5 years she could read at a grade 4 level (test unspecified) using a phonetic approach. An 8-year-old boy was unresponsive, wandered, chanted, and stared. His speech was fragmented and marked by tangential associations, although he was able to read and write before entering kindergarten. Cain stated that attributing savant skills to rote memory is a gross oversimplification, since most such abilities involve many subprocesses and their synthesis. He viewed the skill as the sole realm in which the child might feel competent, in control, and invulnerable.

Huttenlocher and Huttenlocher (1973) reported the developmental histories of 3 cases of hyperlexia. Gross delays, regressions, or abnormalities of speech and language were present in all 3 children. They required their sample to read four two-part and four three-part written directions (for a total of 20 'units'). They also received the same spoken directions. The number of correct responses in the auditory mode ranged from 11 to 19, while the number of correct responses to written instructions ranged from 11 to 17. Huttenlocher and Huttenlocher stressed that early speech in hyperlexic children is marked by echolalia, pronominal reversal, or idioglossia. They believed that the primary difficulty in the disorder is an inability to associate speech sounds with meaning. Thus, despite a relatively intact memory in which the child's ability to retain the speech sound is intact, he has much difficulty associating that sound with meaning. He 'imitates' rather than encodes experience. It is not immediately clear why a child might be able to link a speech sound with one visual stimulus, a letter, but not with another, the object itself. Huttenlocher and Huttenlocher believed that an anatomical defect in the formation of 'connections within the parietal lobes, and possibly, in other cortical areas' ultimately causes the disorder.

Silberberg and Silberberg (1968–69) reported on a 3-year-old girl who exhibited autistic features. She read some words at the age of 1 year and could read 'any' word presented to her by the age of 3 years. The authors believed that word recognition skills could exist 'apart from' general verbal functioning. Hyperlexia may be a matter of 'specific neurological precocity' rather than general intellectual functioning. The nature of the neurological precocity was, unfortunately, not elucidated.

The sample of hyperlexics studied by Mehegan and Dreifuss (1972) consisted of 11 males and 1 female between the ages of 5 and 9 years. All were severely attentionally disordered. Only 1 child could converse meaningfully; the others were dysarthric, echolalic, and perseverative. All instantly and indiscriminately commenced reading any available material, their choice ranging from telephone directories to drug brochures. Attempts to divert the children met with great resistance. The authors noted that 1 child could paraphrase the material in a way that suggested comprehension, and the activities of 2 other children could be directed by written instruction. Mehegan and Dreifuss emphasized the neurological abnormalities that hyperlexic children displayed, including dysarthric speech, echolalia, perseveration, and motor movements that were random or restless. Choreoathetoid movements, along with other bilateral abnormalities in the neurological examination, were often also present. The prenatal and perinatal histories of the children suggested risk. The investigators considered the possibility that reading in this group of neurologically abnormal children may be acquired by different means than in a normal group. They stressed the highly automatic repetition of words by hyperlexic children, but noted that some degree of comprehension was present.

Rosenberger *et al.* (1975) described 4 preschool hyperlexic children. All had abnormal speech development and echolalia was present in 3. The authors reported that neurological examination was normal. Receptive language assessed on the Illinois Test of Psycholinguistic Abilities and the Northwestern Syntax Screening Test was more impaired than expressive language. Reading was with 'some comprehension'. The authors further believed that reading could serve as a compensatory channel for hyperlexics.

Elliott and Needleman (1976) studied a hyperlexic child aged 5.7 years. She was hyperkinetic, had a short attention span, and manifested compulsive behaviour patterns. The child suffered from a complete absence of expressive speech, had poor fine motor coordination, and may have had a mild hearing loss. However, she was able to point to written answers to verbal or written questions regarding category usage. In addition she could match pictures to their written tag. The child was able to respond correctly to 20 one- and two-part written commands and to 'a few' three-part commands. The child's parents first noticed an interest in written words at approximately 1.25 years of age. Later, her reading appeared compulsive, her choice of material ranging from medical charts to children's books. She used a magnetic board to spell out her needs in short phrases and words. Elliott and Needleman thought that hyperlexia was the manifestation of a greatly accelerated cognitive ability to recognize words as linguistic symbols.

Cobrinik (1974) described 6 cases of hyperlexic children who showed motor restlessness, had stilted and isolative behaviour, and had marked abnormalities in speech, typically involving echolalia. Five of the children also had recall of routes and places. The group had a mean Verbal IQ of 56.6, a mean Performance IQ of 59.7, and a mean Full Scale IQ of 55.6 on the WISC. The children, whose mean chronological age was 13.3 years, read words on the Wide Range Achievement Test (WRAT) beyond the grade 4 level. They demonstrated abnormal strengths on the Block Design subtest of the WISC, but had considerably more difficulty expressing their understanding of social situations. On the Illinois Test of Psycholinguistic Ability, the mean Psycholinguistic Age was 5.5 years. They displayed relative strengths in auditory and visual memory and relative weaknesses in auditory reception, association, and grammatic closure. Cobrinik emphasized their highly developed visual recall, later advancing the theory (1982) that acute visual registration and retention resulted in hyperlexia. In support of this theory, he tested the ability of 9 hyperlexic boys to complete a configuration from fragmentary details. The experiment involved the presentation of words which were degraded by the elimination of elements of letters. The hyperlexic children had more success reading the words than did the normal control group. Cobrinik believed that hyperlexic children were able to apprehend large visual configurations rapidly and suggested that the skill was mediated by right hemispheric processes.

Richman and Kitchell (1981) studied 10 children who were considered to be hyperlexic. However, the criteria for defining the disorder were those advocated by Silberberg and Silberberg. In addition, they made no mention as to when and how reading behaviours developed, and all children in the study had WISC Full Scale IQs greater than 90. Thus, it is difficult to determine whether the children studied were at all akin to those described previously.

Denckla (1979) noted that the best preserved language skill in hyperlexic children is the naming of colours and objects on visual confrontation. She further stated that the children can repeat and memorize speech but cannot connect speech sounds with meaning. They are able to connect a visual configuration to a series of phonemes and thus name and read aloud, but have difficulty 'going in the other direction' (producing or identifying a visual configuration from a given phonemic pattern). The exception of spelling to dictation and comprehending intralinguistic speech-sound relations and syntax was noted. Denckla believed the clinical picture of the hyperlexic child was 'strikingly' like that described by Heilman *et al.* (1976) in a case study of transcortical aphasia. The patient of Heilman *et al.* was able to name and repeat but was unable to comprehend speech. He also was able to read aloud without comprehension. However, the authors did not offer data on his reading ability or the process by which he read. Using an aphasic syndrome that results from an acquired lesion is probably not a suitable model for hyperlexia.

Rimland (1964) suggested that savant skills in general (hyperlexia being one) entail extraordinary attention to the precise physical attributes of stimuli. While a normal person has the capacity to attend to exact physical details, he or she may also 'trade off' for a broader band, more general, and abstract style. Thus the person may 'give meaning' to the object of attention. Autistic savants are 'locked into' a narrow, highly focused form of attention with no capacity to 'disattend'. Rimland, in effect, believed that there is complementarity between sharpness of imagery and abstract thought. He suggested that a particular impairment in the reticular formation explains not only the disability of autistic children but also their hypertrophied abilities.

Healy *et al.* (1982) found 'distinct commonality in development' in 12 hyperlexic subjects whom they studied. While gross motor milestones were normal, actions involving patterned motor skill were delayed. Speech was also delayed and echolalia frequently noted. Autism was the most frequent concomitant of hyperlexia. Reading in the children was acquired at about the age of 3 years. Each family was greatly surprised at the development; none had instructed their children. Some children read before they spoke. Comprehension was reported to be limited. Family histories were also consistent in that reading disorders were found on the paternal side in 11 of the 12 families. The children were administered a large battery of tests, which included the McCarthy, Test of Language Development, Wide Range, and subtests from the Detroit Test of Learning Aptitude, as well as Piagetian tasks. In the cognitive area (on the McCarthy Test), a ratio of mental to chronological age was used and the resulting quotients ranged from 37 to 91. Relative strengths were demonstrated in the areas of concrete categorizing and verbal memorization of nonmeaningful strings. Verbal tasks requiring comprehension and meaningful expression led to impaired performance. Piagetian tasks of conservation and seriation were uniformly difficult for the hyperlexic children. Performance on tests involving small units of language was better than on tasks requiring conceptualization of word groups, rules, and relationships. Many problems in the social use of language were evident. Reading grade levels ranged from 3.8 to 11.3 with a median at 7.5 on the Wide Range. While the children could comprehend single words that they read and 'a few' could comprehend short literal sentences, no evidence was found for comparable comprehension of units larger than sentences without pictorial analogues. All the children had success in reading pseudowords. Healy *et al.* believed a link was present between hyperlexia and dyslexia on the basis of familial patterns and 'disordered symbolic relationships'.

The data and views of previous researchers allow for consensus on several features of hyperlexia. Virtually all authors describe abnormal speech development involving primitive or nonexistent conversational speech, dysarthria, echolalia, and perseveration. In addition, all note hyperactivity and/or gross attentional deficits. The other feature which appears to define the condition consistently is the precocious reading of words in the absence of specific instructional experience and other expressive language skills. Less agreement exists as to the degree of comprehension by hyperlexics of what they read. While the absence of comprehension was once considered to be a defining feature, several investigators allude to 'paraphrasing' ability and accurate response to written commands.

Aetiological theories focus on cognitive and/or neurological mechanisms. Deficits in grasping abstract concepts or in associating speech sounds with meaning are often suggested. Alternatively, an innate accelerated ability to recognize linguistic symbols has been proposed. Still others have postulated extremely acute recall of visual stimuli or attention to precise physical attributes of the visual stimuli in hyperlexics. Ego-psychologists describe hyperlexia either as a compensatory mechanism or a maladaptive reaction to environmental conditions.

The association of hyperlexia with pre- and perinatal difficulties and with various neurological symptoms strongly implicates central nervous system involvement, whether it be in the form of neurological precocity or aberrant neurophysiology. Various investigators have suspected deficient functioning in the parietal lobes, the right hemisphere, or the reticular formation.

The major aim of the present study was to delineate the reading process (rather than study abilities correlated with reading) in hyperlexic children. This involved assessment of the employment of phonological and visual routes to the lexicon and to the output stage. In addition, the possible existence of semantic processing was examined. More broadly, reliance on metalinguistic processing was measured. Of further interest was the relation of a higher-order language skill—reading—to brain function. By acquiring information on the above areas it was hoped that we would be in position to speculate on the origins of reading in hyperlexic children.

METHODS

Subjects

The subjects for the present study consisted of 7 boys and 1 girl between the ages of 5.2 and 17.8 years (mean age 9.9 years). Four subjects were Caucasian, 3 were Black, and 1 was of Hispanic background. On the Hollingshead-Redlich Index of Socioeconomic Status, 1 subject was in Class 2, 2 were in Class 3, 3 were in Class 4, and 2 were in Class 5.

All subjects in the study had language delays and difficulties in integrated behaviour and in relating to others. All learned to read with no formal instruction and, with one possible exception (Case 5), before the age of 5 years. Reading ability was uniformly superior to other linguistic abilities.

Case 1 (17.8-year-old female). M.H. was born at term after labour had been induced. The pregnancy was complicated by maternal urinary tract infection. M.H. appeared cyanotic and possibly jaundiced at birth. A severe crib accident at roughly 6 months of age caused extended anoxia and loss of consciousness and interrupted her (to that point) normal development. Subsequent development was delayed both in gross motor and language spheres. She did not walk until 20 months and did not speak words until 3 years of age. Use of sentences occurred one year later. Speech was marked by dysarthria and echolalia and was often cluttered. Reading emerged suddenly at the age of 3 years when she first read billboards. From that time, she began to read any material indiscriminately. Behaviourally, she was active and uncontrollable as a toddler, requiring a neuroleptic to settle her. She later improved, and currently interacts with others. She still exhibits abnormal behaviour, including overeating, self-injury (biting her arm), and enuresis. Stimulant medication (methylphenidate and dextroamphetamine), anxiolytic medication (diazepam), and a neuroleptic (thioridazine) have also been employed. M.H. has received special education since the age of 2.5 years in a language development programme, a developmental classroom, and a neuromuscular patterning programme.

Neurological examination was performed on several occasions. Initially she exhibited strabismus and a gait abnormality, but no pathological reflexes. Her sleep patterns were grossly disturbed. A later examination when aged 8.9 years revealed brisk tendon reflexes, bilateral flexor plantar responses, 'poor coordination', and a bilateral intention tremor on a finger-to-nose targeting task. A more recent neurological examination performed when M.H. was aged 16.1 years revealed the presence of a clumsy gait and bilateral intention tremor, but no pathological reflexes. Since the age of 15 years she has suffered from generalized seizures. An EEG indicated that in the waking state there were minor nonspecific paroxysmal features.

Psychometric testing was completed on two occasions. When aged 2.5 years she achieved an IQ of 80 on a test of receptive vocabulary (Peabody Picture Vocabulary Test). Intelligence testing (WISC-R) performed at the age of 13.7 years elicited a Verbal IQ of 81, a Performance IQ of 68, and a Full Scale IQ of 72. Two assessments of reading ability indicated grade 2 ability at 6.8 years and grade 4 ability at age 8.9 years (test intruments were unspecified). Incomplete comprehension was evident. Handwriting was illegible and mathematical skills were poor. During the recent evaluation speech abnormalities were noted. In addition, her social skills were extremely 'awkward'. When frustrated, she attempted to bite her arm. She was quite distractible. However, she was able to converse readily, spoke spontaneously, and displayed a sense of humour.

Case 2 (6.8-year-old male). D.M. was born at full term. There were no pre- or perinatal complications. He attained gross motor milestones precociously. However, language was severely delayed. He did not speak words until 3 years of age, and two-word combinations until 5 years of age. He has had no seizures, tics, or disorders of gait. He underwent surgery for cryptorchism. D.M.'s activity level has always been high. He began to read words abruptly at about the age when he first spoke words, that is, 3 years. The first word he read, according to his mother, was 'Jesus'. His mother also reported that he received limited instruction from an elder sibling. He prefers to read story books, although apparently comprehending little of what he reads.

During the recent evaluation, language was marked by echolalia and a cluttered prosody pattern. D.M. enjoyed tactile stimulation and responded to praise or selected comments by smiling and clapping. He was extremely distractible and often had to be redirected to the task at hand. Conversation was difficult to maintain, although it was possible to engage in reciprocal verbal transactions. Speech was telegraphic. At times he compulsively read labels of games that were not related to the test materials.

Case 3 (8.8-year-old male). C.K. was born at full term without pre- or perinatal complications. He appeared to develop well until 6 months of age. At that time he began to become more isolated and would watch television for long periods of time. Speech and language were markedly delayed. He did not speak words until the age of 6 years when he began echoing what he heard. He has never produced sentences and language is not used communicatively. He refers to himself as 'C'. In addition, gross motor milestones were delayed, with walking occurring at 14 months. Medical and neurological histories are unremarkable, according to his mother. He showed little interest in toys; instead he enjoyed listening to records or music for long periods of time. In addition, he spun objects. He showed little interest in people around him. Reading emerged suddenly at the age of 3.5 years. He first read TV guides and then began to read any printed material.

Although he usually gives no indication of comprehension, he can respond to some written commands. During an earlier psychiatric examination he exhibited echolalia. His behaviour was often perseverative, as when drawing. He followed written instructions at times and had no difficulty reading. He did not appear to have understanding of content. Eye contact was fleeting.

During the current evaluation he was not able to converse spontaneously or reciprocally. It was difficult to make emotional contact with him and he generally remained aloof from interpersonal transactions. He was able to sit and attend for extended periods, although redirection was necesssary.

Case 4 (5.3-year-old male). D.S. was born at term without pre- or perinatal complications. Early medical history was uneventful with the exception of an episode of gastroenteritis. While motor milestones were achieved within normal limits, he did not speak words spontaneously until the age of 4 years. His speech was always characterized by echolalia, dysarthria, and cluttered prosody. He has never demonstrated conversational speech but is able to make known his needs or wants. He reportedly began to read words long before spontaneous speech appeared. He initially read TV guides but later developed an interest in books, newspapers, or other printed material. Comprehension is said to be minimal.

D.S. has a history of isolative and withdrawn behaviour. He does not initiate play or interactions with others. Although he imitates, he does not perform social actions spontaneously and avoids eye contact. He watches television commercials intently, but not cartoons. He often repeats jingles, rhymes, or entire advertisements. He has received formal language therapy since the age of 1.5 years.

Psychometric testing performed when aged 4.5 years revealed average nonverbal intelligence (Leiter IQ = 99), but receptive language abilities in the moderately retarded range (Peabody IQ = 48). An earlier audiometric examination indicated normal hearing.

During the current evaluation he could not carry on a conversation, although he often spontaneously recited TV commercials. At times he became uncooperative or attempted to leave his seat. He responded well to limits and could attend for long periods of time when the task interested him. He was able to check his work and make those corrections that were required. Social interaction skills were generally minimal.

Case 5 (12.6-year-old male). T.M. was postmature by three weeks, but without other pre- or perinatal complications. While gross motor development was within normal limits, training of bladder control was difficult and not fully achieved until 9 years of age. His speech development was markedly delayed as single words appeared when aged 3.5 years. Echoing was the only form of speech exhibited until roughly one year later, when limited spontaneous speech suddenly appeared and echoing diminished. However, at the age of 6 years his speech was still characterized by echolalia and pronominal reversals. Continued improvement resulted in speech that was fragmented, at best, by the age of 9.7 years. Reading emerged gradually at the point when echolalia was diminishing. Initially he was interested in books about animals but then developed a fascination for books about science, nature, and astronomy. His parents believed that he always read with some comprehension.

Unusual behaviour was noted early on as T.M. engaged in hand flapping and played with dust made visible in sunlight. His parents also observed a strong interest in turning pages of books, apparently for the sake of sensory stimulation. Isolative behaviour, disinterest in human contact, avoidance of eye contact, and an obsessional need for constancy in his environment led to a diagnosis of autism at the age of 6 years and to an eventual placement in a school for autistic children at the age of 9. Medical history was unremarkable. Neurological examination was unremarkable with the exception of 'idiopathic toe walking'. However, T.M. did exhibit behaviour suggesting a short attention span and extreme distractibility. He was treated with methylphenidate.

Psychological testing at the age of 11.1 years revealed that T.M. had a WISC-R Full Scale IQ of 76, a Performance IQ of 93, and a Verbal IQ of 64. Achievement at that point on the WRAT was at a grade 4.5 level in reading and 2.7 level in arithmetic. Three years before this, he had performed within the average range on the Leiter International Performance Scale. Visual motor performance was below the tenth percentile on the Bender. During the current evaluation, T.M. was distant and aloof. He was, however, able to maintain a conversation at a concrete level.

Case 6 (10.1-year-old male). C.R. was born at term without pre- or perinatal complications. Although gross motor milestones were normal, he was not toilet trained until aged 3.5 years and did not speak words until aged 3.5 years. Sentences emerged at the age of 6 years and conversational speech two years later. However, speech was characterized by dysarthria, echolalia, and cluttered prosody in the early years. With age, echolalia diminished, but he still had difficulty expressing thoughts. Intrusion of irrelevant, inappropriate, and stereotyped phrases occurred. His parents noted that he had proficient nonverbal communication skills by the age of 3 years. He commenced reading suddenly at about 2 years of age when he began reading billboards. By the preschool years he read everything he could, but seemed to comprehend little. His parents observed that he slowly lost interest in reading and began to comprehend better as he grew older.

C.R.'s medical history includes chronic otitis media treated by multiple myringotomy procedures. Neurological examination on numerous occasions, including EEGs, was negative according to his parents. At one time he had been treated for overactive, distractible, and impulsive behaviour.

Since early childhood, C.R. has preferred to play indoors by himself. He showed little interest in toys or symbolic play. He never developed peer associations. While he established little eye contact as a toddler, he has progressively improved. His education has included placement in a classroom for language-impaired children with attempts at mainstreaming in the upper grade school years.

Psychometric testing indicated that he had an IQ of 59 when he was a preschooler. Subsequent testings revealed improvement with estimates of Full Scale IQ of 89 and, finally, 100. Verbally he scored best on a test of knowledge and retrieval of general information. On an achievement test, the Peabody Individual Achievement Test, he was able adequately to describe verbally how a pictorial analogue was related to a sentence that he had read. Visual motor skills, assessed by the Visual-Motor Integration Test, were at the 8.5-year-old level.

When C.R. was assessed in the present study at the age of 10.1 years, it was noted that eye contact had improved. However, he tended to interrupt a verbal exchange with irrelevant statements or to perseverate on certain topics or phrases. For example, when praised he would add that he had done 'very well'.

In general, oral reading skills were well developed. Overall, current observation of improved language and communication skills was confirmed. He was able to maintain better eye contact, initiate appropriate conversation, and responded appropriately in verbal exchanges a great portion of the time. Distractibility represented a continuing problem. In addition, he was still relatively unable to relate to peers.

Case 7 (5.2-year-old male). L.N. was born at full term without pre- or perinatal complications. He walked at about 2 years of age and spoke spontaneously at about 3 years of age. Speech was difficult to comprehend and dysarthric due to cluttered prosody. However, he abruptly began to read single words at approximately 3 years of age without any instruction. Initially he read TV guides but subsequently began to read magazines, books, and packaged food labels. Eating and sleeping habits were poor; overactivity with a short attention span was evident, and peer relations were problematic. Medical history includes only one minor surgical procedure to correct a hernia. Neurological examination was normal.

At 4.5 years of age L.N. received a language evaluation which indicated abnormal receptive language skills. On the Peabody Receptive Vocabulary Test he obtained a Mental Age of 2.67 years. Expressive language was disrupted by echolalia, restricted vocabulary, and short mean length of utterance. Overall, his use of language was telegraphic, with few function words. However, he was able to form simple 'wh' questions and negative structures and pronoun use was appropriate. At 4.6 years of age he obtained a Mental Age of 4.0 years on the Leiter International Performance Scale. In general, he did better on conceptual nonverbal tasks than he did on purely perceptual motor tasks. Visual motor development, as assessed by a task in which he was requested to draw shapes, was at the 4.5 year level. During the evaluation he read words in a driven and compulsive fashion. He appeared to understand individual concrete words but not more complicated phrases. Articulation was poor.

During the present evaluation, L.N. was extremely active and had difficulty remaining seated. His attention was easily captured by extraneous visual stimuli. When fatigued, he spontaneously wrote words on a blackboard which he then read. He did not initiate conversational speech.

Case 8 (12.4-year-old male). A.C. was born at term after labour had been induced. The prenatal history was complicated by his mother's emotional problems which necessitated treatment with chlordiazepoxide. A.C. was anoxic at birth, requiring oxygen and incubation. Subsequent gross motor development was normal. However, speech was markedly delayed. He began echoing single words at the age of 3 years. Simple two-word phrases emerged within 6 months, but communicative or conversational speech first appeared at the age of 7 years. Echolalia and pronominal reversals persisted throughout the development of language skills. His medical history includes an admission to hospital when aged 4 months because of severe dehydration. Since the age of 2 years his sleep patterns have been disturbed. He did not demonstrate hand preference until roughly 8 years of age. His EEG has been normal.

His parents report that A.C. began to read words suddenly when aged 2 years while attending to sets of record books. As a toddler he was interested in colouring books, primarily for the printed words that they contained. His parents felt that he always comprehended some of what he read. At the age 11 years he began teaching himself to read Spanish.

Since he was an infant A.C. disliked being held and showed little interest in social contact. He often rocked or had uncontrollable behavioural outbursts. By the age of 4 years he was diagnosed as autistic. Symbolic and social play were not evident until the age of 11 years.

Psychometric testing at the age of 9.5 years showed that his nonverbal Performance IQ fell in the Low Average range (IQ = 86). Assessment of academic skills indicated seventh grade level reading ability, third grade level spelling, and first grade level arithmetic skills. When aged 12.3 years nonverbal intelligence fell in the Mildly Retarded Range using a different test (Leiter International Performance Scale IQ = 54). Receptive vocabulary skills were at the 4.9-year-old level on the Peabody Picture Vocabulary Test.

A.C.'s behaviour during the current evaluation was marked by intense periods of anxiety. It was, however, possible to engage him in tasks during these affective storms and he would begin to work again. Separation from his parents seemed to affect him adversely and he often attempted to leave the room. In addition, his attention span was short. He was aloof interpersonally and made no effort to relate to the investigators. No conversational speech was evident. He was observed to echo speech. When very agitated, he began hitting his head with his hand while stating 'Don't hit your head!'.

Instruments

Intelligence tests. Three different intelligence tests from the Wechsler series were used to assess the subjects' cognitive functioning in specified areas. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) was used for subjects aged 4.5 to 6.5 years (2); the Wechsler Intelligence Scale for Children-Revised (WISC-R) was used for subjects aged 6 to 17 years (5) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was used for 1 subject over 17 years of age (Wechsler, 1963, 1974, 1981). All scales in the series are standardized across a national sample of children or adults representative of the general population in the United States.

For the present study 4 subtests were administered to each subject. While analogous subtests employ variations in content (in order to allow age-appropriate items), the form of the analogous subtests is identical (with two exceptions). Two subtests were drawn from the Verbal Scale. In addition, 2 from the Performance Scale were also administered. (1) The Vocabulary (V) subtest of the WPPSI, WISC-R, and WAIS-R assesses word knowledge and linguistic faculty in defining words. (2) The Digit Span (DS) subtest of the WISC-R and WAIS-R is a test of immediate memory in which digits are repeated. The analogous subtest of the WPPSI (Sentences) requires the child to repeat exactly sentences of increasing length. Two subtests were drawn from the Performance Scale. (3) The Block Design (BD) subtest of the WPPSI, WISC-R, and WAIS-R requires the child to arrange blocks to match an abstract design on a card or of a model. (4) The Digit Symbol subtest of the WAIS-R, the coding subtest of the WISC-R, and the Animal House subtest of the WPPSI (CO) are analogous subtests with age-graded variations in format which assess symbol-association learning. At the younger ages (WPPSI), coloured pegs must be matched correctly to pictures of animals *via* a key. Slightly older children (6 to 7 years of age on the WISC-R) must match meaningless markings to geometric shapes. School-age children (8 years and upwards on the WISC-R) and adults (WAIS-R) must match shapes to digits (1 to 9), again *via* a key.

Raw scores were based on the number of terms responded to correctly (for BD and CO 'bonus' points are awarded for rapid performance). Raw scores (R) were then converted to age-dependent Scaled Scores (SS) (population $\bar{X} = 10$, SD = 3).

Achievement tests. For the purpose of assessing academic abilities of subjects, the Peabody Individual Achievement Test (PIAT, Dunn and Markwardt, 1970) was used. Subjects (ages 6 to 18.3 years) were compared with the 1967 standardized sample (representative of the national population of school children in the United States) in order to derive age-equivalents, grade-equivalents (G), standard scores, and percentile ranks (P) based upon age and/or level of performance. These may be obtained individually for each subtest of the scale. For the present study 4 subtests were used. (1) The Mathematics subtest (PIATM) assesses skills ranging from matching, discriminating, and recognizing numerals at the youngest levels to difficult mathematical problems at the older levels. A mathematical problem was read to the subject, who then selected the correct (written) answer from 4 options. (2) The Reading Recognition subtest (PIATRR) requires subjects to match letters, and name letters at the youngest levels, and then to read aloud individual words. (3) The Reading Comprehension subtest (PIATRC) requires the subject to read sentences of increasing difficulty silently and then to select the appropriate picture depicting the meaning of the sentence from among 4 choices. (4) The Spelling (PIATSP) subtest requires subjects to select the written equivalent among 4 options of letter names, letter sounds, or (primarily) words spoken by the examiner. For words, foils often were visually similar or pseudohomophonic to the real word.

Authors of the test report median (across different ages) test-retest reliabilities of 0.74 for Mathematics, 0.89 for Reading Recognition, 0.64 for Reading Comprehension, and 0.65 for Spelling. The test appears equally reliable across ages (median = 0.78; range = 0.74 to 0.80).

Specialized tests. Skills involving comprehension of spoken language, paragraph reading and comprehension, and reading of words (of various linguistic classes, including length, frequency, imageability, and orthographic regularity) and pseudowords were assessed. Words were typed on white labels using Prestige Pica typescript with spacing set at 10. (Unless otherwise noted, the labels were affixed to 5 × 7 inch unlined white index cards.) Presentation order was random within a given test.

Token Test. The subjects were requested to perform simple orally presented commands that involved comprehension of syntax and sequencing (e.g., 'Touch the black square after you touch the small circle'). Scores were based upon the number of correct responses to 16 items (Spellacy and Spreen, 1969).

Numbers. The subject read aloud words representing the numbers 1 to 20. Responses were scored as correct or incorrect.

'Inconsistent' Pairs. Ten pairs of words constituted the list. Each pair consisted of words with identical orthographic strings which, however, mapped to contrasting phonemes. For example, 'grown' and 'gown', 'simply' and 'imply', 'march' and 'monarch' were grouped. Upon presentation words were randomized with the constraint that two members of a pair could not occur in succession. Scores were based on the total number of words read correctly (PAIR TOT) and the number of pairs read correctly (CONCORD RIGHT). In addition, data were available on pairs in which numbers were both read incorrectly (CONCORD WRONG) and on pairs in which one member was read correctly and the other incorrectly (DISCORD). The test was designed to assess reliance on rule-based grapheme-phoneme decoding processes.

Frequency × Imagery. This word set consisted of 100 words, 25 in each of four categories: High Frequency-High Imagery (HFHI); Low Frequency-High Imagery (LFHI); High Frequency-Low Imagery (HFLI); and Low Frequency-Low Imagery (LFLI). High-frequency words were defined by inclusion among the A or AA words in the Thorndike and Lorge list (1944), while low-frequency words were culled from non-A or AA words. High and low imagery words were defined by ratings of greater than 5 and less than 5, respectively, on the Paivio *et al.* (1968) list. Subjects were required to read each word aloud. Word order was random. Scoring was based on the number read correctly within each condition. The test was designed to measure the effects of frequency and imagery on reading.

Phonological Sounds. Words in the list were paired so that specified parts of the words either matched or did not match either graphemically and/or phonetically. Four conditions were created with 5 word pairs in each condition: (1) word pairs in which the specified segments were graphemically identical and phonetically identical (SS) (e.g., choice–child); (2) graphemically identical but phonetically dissimilar (SD) (goal–gem); (3) graphemically different but phonetically identical (DS) (cry–mile); and (4) graphemically different and phonetically different (DD) (call–say). Subjects were required to read each work on the card aloud and then to indicate whether the underlined segments of the two words 'sounded the same or sounded different'. Note that paired words occurred together on the same card. Presentation of the word pairs was random. The test was designed to assess metalinguistic awareness and conceptualization in the reading process.

Function Words. Forty-six function words constituted this set (e.g., but, of, between). Subjects read each word aloud and the score was based upon the total correct.

Nonsense Words. This set consisted of 25 one-syllable (PWS) (e.g. nur, pess, geet) and 25 two-syllable (PWL) (nonter, ribbat, bomper) nonsense words. All nonsense words were pronounceable. None were pseudohomophones. Subjects read each word aloud after being informed that they were reading 'fake' or 'made-up' words.

Lexical Decision. This set (LEXDEC) consisted of 25 real, high-frequency (A or AA) nouns and 25 pronounceable pseudowords randomly presented. The real words were further subdivided so that there were 13 high-image and 12 low-image words. Both real words and pseudowords were of one or two syllables. Subjects were asked to read each word aloud and then indicate whether the word was 'real' or not. Scores were based on the total number of correct decisions (OVERALL), and correct decisions on low-imagery words (LIWD), high-imagery words (HIWD), and pseudowords (PWD). The test was designed to assess metalinguistic knowledge.

PPVT Pseudohomophones. The standard Peabody Picture Vocabulary Test (PPVT) (Dunn, 1965) format was varied. The major alteration consisted of 35 printed pseudowords homophonic to the actual PPVT words (Saffran and Marin, 1977). The subject was required to select the appropriate picture from among 4 choices which corresponded to the printed pseudohomophone For example, presented the written pseudohomophone 'kloun', the subject was to select a picture of a clown over 3 incorrect pictures. Two control conditions were also created. First, for an equal number of items throughout the range of test items used, the standard PPVT administration was also employed. Thus a word was spoken to each subject (e.g., 'car') and the subject was to respond by selecting that corresponding picture (out of 4). When errors were made on the (printed) pseudohomophone words, the printed real word was immediately presented. Scoring consisted of the total number of correct semantic selections under each condition (PPVT and PPVTPHP). The percentage of real words read correctly after initial failure on the PPVTPHP task was computed (PPVTPHP-RW DIF). The test was devised to expose the interplay between auditory, phonologic, and visual access to the semantic lexicon

Durrell Test. The standard administration format of the Durrell Analysis of Reading Difficulty (Durrell, 1955) was altered slightly. Paragraphs corresponding to grade levels 1 to 8 were typed on pages. Questions relating to each paragraph were typed below the paragraph. Subjects read aloud only the paragraph at the grade level indicated by their PIAT Reading Recognition score. The questions were then read to the subjects with the paragraph available for reference. Subjects were scored only on the percentage of correct responses (DRRLCOMP) to questions.

Pseudoword Recognition. This test examined the subject's ability to spell nonsense words. In the first part, the subject was presented with a card with 4 nonsense words printed horizontally (e.g., peb, mib, pib, lem). The target word (e.g., pib) was then read to the subject, who was to point to the correct word from among the 4 choices. The second part of this test required the subject to read a nonsense word silently. The experimenter then spoke 4 pseudowords, 1 of which matched the target word. The subject listened and then made a signal when the correct pseudoword was spoken. Each part of this test (PWSPEL and PWREAD) consisted of 10 items.

Altered Paragraphs. The grade 4 level paragraphs of the Gray Oral Reading Test were altered by changing punctuation marks, namely, periods. In the initial paragraph, periods were added to sentences in places which might be considered appropriate in the English language. For example, the first sentence of the normal paragraph which reads 'One day five children went out to play in the beautiful white snow' was altered to read 'One day five children went out. To play in the beautiful white snow'. Three such changes were made.

The second paragraph was altered so that it contained 5 periods in grossly inappropriate places. The initial sentence of the unaltered paragraph, which reads 'One of the animals was a dog' was altered to read 'One of the. Animals was a dog'. A total of 5 periods was added to this paragraph to make a total of 9 periods in the second altered paragraph.

The paragraphs were presented both in altered (ALTPAR) and unaltered (PAR) forms at different times (T_1, T_2, and T_3). At T_1 only the altered paragraphs were read and the amount of time for the readings (of each paragraph) was recorded. At T_2 the unaltered paragraphs were read, followed by both altered paragraphs at T_3. Times were recorded for each paragraph separately.

Visually Deviant Words. Six words were distorted visually through alterations of case (VDWC) (HOme), 6 through orientation (VDWO) $\begin{pmatrix}\text{c}\\\text{r}\\\text{y}\end{pmatrix}$, 6 through linearity (VDWL) (lo$^{\text{n}}{}_{\text{g}}$), and 6 through spacing (VDWS) (kit t en). Six more were distorted by the addition of plus (+) signs (VDW+) (g+o+o+d). Subjects were instructed to read the words. Only correct pronunciations within a time limit of 3 s were scored as correct. The test was designed to assess reliance on visual 'gestalt' processing and disattention disabilities.

Word Length. Twenty-five short (one syllable) words and 25 long (more than one syllable) words constituted this list (WS and WL). All words were of high frequency (A or AA). Subjects read each word aloud. Scoring was based upon the number of words read aloud correctly in each condition.

Irregular Spellings. Twenty-five words with unusual spellings were included in this list (EXCEP), each of which employs exceptional grapheme-phoneme conversion rules (e.g., colonel, yacht). Subjects read each word aloud and responses were coded as correct or incorrect.

Altered Paragraphs (T_2 and T_3). *See* description above.

Forced Choice Error. First the subjects were presented with a single target word which they were to read silently. (Most subjects were unable to abstain from reading aloud.) Next, they were shown a card with 3 foils from which they were to choose the word 'most like' the target word (which was no longer in view) (FORCED CHOICE). The 3 foils varied in the manner of similarity to the key word. (1) Visually similar words were more similar graphemically than phonetically. (2) Phonetically similar words were homonyms of the keyword. (3) Semantically similar words resembled the keyword only in meaning or in associative value; for example, the keyword 'sail' had the visual choice-word 'said', the phonetic choice-word 'sale', and the semantic choice-word 'boat'. Order of the choice-words was random. The task was designed to assess preference in decoding.

Procedure

The subjects were seen individually at the Children's Hospital of Michigan and were administered the tests in the order in which they were described above. Each task was introduced with standard instructions to the subject, but when necessary the instructions were repeated or paraphrased in order to obtain appropriate task behaviour. Frequent breaks were necessary for most subjects because of fatigue and/or short attention spans. Thus, although the entire battery could have been completed in about 2 h, it usually took 3 h or more to complete. All sessions were either audiotaped or videotaped for subsequent data analysis.

Parents were interviewed regarding their child's developmental history, reading experiences, and general background. The period for interviewing the parent was used as a 'break' from testing for the child.

Error Analysis

Reading tests (Inconsistent Pairs, Frequency × Imagery, Word Length, and Irregular Spellings) were analysed for the type of pronunciation errors committed while reading. According to the scheme presented by Patterson (1981), errors were coded as visual paralexias, phonological paralexias, derivational paralexias, or semantic paralexias. A fifth category was composed of mumbled, incoherent, or nonsensical pronunciations. Visual paralexias involved substituting a real English word for the actual word, on the basis of visual similarity (e.g., reign–'region'). Phonological paralexias involved a mispronunciation of the word caused by (explicable by) the rules of phonics (glove–'glōve'). A semantic paralexia involved substituting a real word of similar meaning for the actual word (oven–'stove'). Derivational paralexias involved adding or subtracting word prefixes or suffixes (e.g., unhappy–'happy'). Video and audiotapes were reviewed in order to conduct this analysis.

RESULTS

Standardized Tests

The descriptive results of the standardized tests are presented in Table 1. Of the WISC-R variables, the hyperlexic children did best on the Block Design subtest. They had considerably more difficulty in expressive Vocabulary, Coding, and Digit Span. It should be noted that all scores were below the mean of the standardization sample (10). Regarding PIAT performances, percentiles in Reading Recognition, Reading Comprehension, and Spelling tended to be high, reflecting precocious ability in the younger children of the sample. However, the range of performance in terms of grade level was narrow (e.g., Reading Recognition spread from 2.8 to 6.4). Performance in Mathematics was uniformly depressed. The difference between the group means in Reading Comprehension and Reading Recognition was not significant ($t = 1.88$, $P = 0.102$).

Reading

As listed in Table 2, the hyperlexic children had no difficulty reading numbers or reading function words. Mean scores were 18.75 (of 20) and 42.625 (of 46), respectively.

A two-way analysis of variance was used to analyse the effects of frequency (high and low) and imagery (high and low) on oral reading. Highly significant main effects were found. High-imagery words (41.875/50) were read better than low-imagery words (34.125/50); high-frequency words (40.625/50) were read better than low-frequency words (35.375/50). No interaction was present. Tables 3 and 4 summarize the results.

An error analysis of the data was also performed (*see* Table 5). No semantic paralexias were elicited. Nonspecific errors (inchoate or nonsensical) were most common. Of meaningful errors, those of the visual type were most common (0.2822). They were not, however, associated with the linguistic variable of imagery (imagery [high/low] × error [visual/all other]; test of association: $\chi^2 = 0.4264$, $P = 0.52$, $df = 1$), nor with frequency ($\chi^2 = 0.8700$, $P = 0.38$, $df = 1$). Phonological errors were relatively uncommon, comprising 0.1209 of all errors. However, a trend toward finding fewer phonological errors in low-imagery words was found (imagery × error: $\chi^2 = 2.6284$, $P = 0.11$, df = 1). Derivational errors were rare (0.0320).

The number of syllables, whether in a word or pseudowords had a significant effect on the reading of hyperlexic children. Student t-tests indicated that short real words were read correctly significantly more often than long real words (t = 3.04, $P = 0.02$) and that short pseudowords were read more accurately than long pseudowords (t = 3.43, $P = 0.01$). Implicit in the analysis regarding pseudowords is the finding that hyperlexic children are able to read them with success (55 per cent). The results are presented in Table 6.

With regard to error types (for real words, short and long), nonspecific mistakes were most common. No semantic paralexias were noted and derivational errors were rare (0.0434). More visual errors (0.2173) were made than phonological errors (0.1304).

Reading recognition and spelling recognition of pseudowords were assessed. The results are given in Table 7. While the hyperlexic children were proficient in matching the spoken word to 1 of 4 written pseudowords (averaging 8.125 of 12), 3 were unable to perform the pseudoword reading recognition subtests (in which they read a word silently, then indicated which 1 of 4 was spoken correctly). Of the 5 that were able to perform, skills were also proficient (averaging 9.33 of 12).

Of 10 pairs or words with inconsistent and contrasting pronunciations of identical grapheme clusters (e.g. march-monarch), the hyperlexic children read 10.750 of the individual words. The group was able to read on the average 3.0 pairs correctly. Of a total of 35 errors occurring when pair responses were discordant, 11 (0.3114) were made to the more regular and 24 (0.6857) to the less regular member of each pair. However, the effects of word frequency may have influenced the results, the more regular words being more frequent. Visual paralexias accounted for 0.2353 of errors in this condition, phonological paralexias for 0.5714 of errors. When both members of a pair were read incorrectly, visual and rule bound phonological errors were of equal frequency. Words that were highly irregular in spelling ('exception words') presented minor difficulties for the hyperlexic children. They read on the average 14.625 of 25 correctly (*see* Table 8).

Error analysis (150 errors possible, 60 errors made) was performed on the data of 6 subjects. Phonological errors were most common (0.6833), followed by visual errors (0.2500). Nonspecific errors were uncommon (0.1666), derivations and semantic paralexias nonexistent. Of interest was the finding that the 3 subjects who had the greatest success in the task made a considerably higher proportion of visual errors (8/25 = 0.3200) than did those subjects who had less success (2/35 = 0.0571).

Comprehension

Results on tasks assessing comprehension are shown in Table 9. Auditory comprehension of spoken language was assessed on the Token Test. Of the 16 items the hyperlexic children responded correctly to approximately 50 per cent. None of the children performed flawlessly, even though those 4 subjects beyond 10 years of age would have been expected to do so.

Auditory comprehension of spoken words on the Peabody Picture Vocabulary Test was also assessed. The hyperlexic children were able to choose (on the average) the correct visual analogue in 25.331 of 35 cases. When they were required to read a pseudohomophone prior to choosing its pictorial analogue, performance decreased slightly to a mean of 21.175. However, the difference between the spoken and pseudohomophonic reading version of the task was not significant ($t = -1.32$, $P = 0.23$). If the hyperlexic children could not make the correct selection on the pseudohomophone task, they were required to read the real word and select the pictorial analogue. Success was at the 42.250 per cent level. Inspection of the data revealed that the performance of the 2 children with the highest comprehension improved the most with the written presentation of the real word.

After reading a paragraph on the Durrell Test (at Reading Recognition grade level), the hyperlexic children were questioned about it. Items were presented simultaneously in written and spoken modes. The group was able to respond (verbally) correctly only to 33.3 per cent of the queries.

In a forced-choice paradigm, the hyperlexic children had the opportunity to respond on the basis of meaning. They did not. Analysis of χ^2 procedures indicates that the differences between the 3 possibilities (visual, semantic, or phonological) related to the target word nearly reached significance ($\chi^2 = 5.677$, df $= 2$, $P = 0.0615$). The finding probably results from the high frequency (11.625 to 3.500 to 4.875) with which the 'phonologically similar' items were chosen.

Metalinguistic Knowledge

Metalinguistic knowledge in reading was assessed through two different tasks. The data are listed in Table 10. On a lexical decision task 3 hyperlexic children averaged 45 correct responses to the 25 real and 25 pseudowords. In addition, they did better responding to real high-imagery words than real low-imagery words. No trends were evident in error analysis of false positive and false negative responses. Of greater import was the inability of 5 hyperlexic children to grasp the nature of the task. On the grapheme-phonologic sounds conception tasks which required the children to indicate whether a grapheme (or graphemic cluster) had the same or different pronunciation in two different words, only 3 hyperlexic children were able to grasp the nature of the task. The 5 hyperlexic children who could not complete the task also could not perform on the lexical decision task. Those who were able to do the task appeared to display a response bias towards 'different'. The very limited sample size precluded the use of inferential statistics.

Disturbances of the Reading Process

Altering punctuation (by incorrect placement of periods) did not have a significant effect on paragraph reading as shown in Student t-test comparisons (*see* Table 11). In the first such contrast, the difference in seconds between reading a correctly punctuated paragraph and a 'mildly' incorrectly punctuated paragraph (4.33 s) and the difference between a second correctly punctuated paragraph (7.33 s) was not significant (t = 0.81, $P = 0.454$). In the second, the total time in seconds it took the hyperlexic children to read the two normally punctuated paragraphs (22.67 s) was shorter than the time it took them to reread the same paragraphs with incorrect punctuation (38.50 s), despite the latter being read last. However, the difference was not significant (t = 1.17, $P = 0.293$).

Only words made visually deviant by the addition of plus (+) symbols led to a decrement in performance (*see* Table 11). The mean score was 2.0 of a possible 6, while means for the other conditions in which linearity, case, spacing, and orientation were disturbed ranged from 4.625 to 5.250 (out of a possible 6). Repeated-measures analysis of variance indicated a significant within-subject between-measures effect (F (32, 4) = 16.021, $P = 0.000$).

Correlations

Age correlated with nearly all cognitive, achievement, and comprehension variables at or near significant levels when raw scores or raw score equivalents (e.g., grades) were used as units of measurement. However, correlations with Scaled Scores or percentiles were negative or low. Table 12 displays the results.

Correlations among cognitive abilities as assessed by the WISC-R subtests tended to be low. None approached significance (*see* Table 13). Neither did any of the WISC-R subtests correlate significantly in a positive direction with various measures of reading ability. The results are presented in Table 14.

Table 15 displays the correlation matrix of the PIAT. Reading Recognition performance correlated significantly with Spelling but not with Mathematics or Reading Comprehension. Correlations among Spelling, Mathematics, and Reading Comprehension were high. From Table 16 it can be seen that Reading Recognition consistently correlated highly with reading different classes of words and pseudowords. Both Mathematics and Reading Comprehension correlated highly with reading words, but not pseudowords. Reading ability on visually deviant words was not associated with other achievement abilities. A finding of interest was a relatively low correlation between Reading Recognition and comprehension and cognitive abilities.

There were no patterns evident in the intercorrelations among tasks assessing word length or word regularity. The results are shown in Table 17.

Performance on the Token Test was not associated with those cognitive abilities assessed by the WISC-R. However, it was highly associated with work on the PIAT (with the exception of Reading Recognition), reading involving lexical access, and various other measures of comprehension. The results are listed in Table 18. In addition, the ability to perform (regardless of level) on tests of metalinguistic awareness, namely lexical decision and grapheme-phoneme rule knowledge, is highly associated with Token Test performance (above or below the mean) (*see* Table 19).

A correlation matrix consisting of various tests of reading and auditory comprehension is presented in Table 20. In general the performance on auditory receptive vocabulary (PPVT) was not associated with performance on the other tasks. However, measures of comprehension in reading were highly correlated. (The Token Test, another instrument assessing auditory comprehension, was highly correlated with measures of reading comprehension.)

DISCUSSION

General Findings

The WISC-R pattern displayed by the hyperlexic children is consistent with the pattern found in autistic children. That is, Block Design is typically among the highest Scaled Scores, while Vocabulary is among the lowest (Lockyer and Rutter, 1970). In addition, Digit Span, a task of short-term verbal memory, was consistently subnormal. Therefore, it is unlikely that exceptional retention abilities for verbal material play a part in hyperlexia. Moreover, the WISC-R performances tended to be independent of one another, in contrast to normals, and were unrelated to reading abilities. On the standardized achievement test, the PIAT Reading Recognition, performance decelerated with age. The actual grade range exhibited was rather narrow despite a wide age range. The majority of subjects did not progress beyond the grade 4 level, a point at which normal children 'read to learn'. Mathematical skills were consistently low. None of the children displayed an unusual ability in this area. Performances in Reading Comprehension and Reading Recognition with individuals were not highly correlated, and the difference between the group mean for Reading Comprehension and the group mean for Reading Recognition approached, but did not attain, significance.

Regarding Comprehension

The Token Test was associated with PIAT Reading Comprehension, Durrell Comprehension (of paragraphs that were read), and comprehension of single words, whether they were presented in pseudohomophonic form or in spoken form. However, reading comprehension of sentences was inconsistently associated with other tasks of reading and auditory comprehension. Of note also was the observation that hyperlexic children increased their performance level when they read real words rather than pseudohomophonic words to gain access to the semantic lexicon. (Schizophrenic adolescents, on a similar task, were able to increase their performance even more markedly. It is likely that they have a larger lexicon and are able to use it (Goldberg, 1984).) The hyperlexic children tended not to alter their choices when errors were made under both conditions; thus, guesses were not based on a narrowed response set. The findings imply that hyperlexic children have access to the semantic sphere *via* both the visual and phonologic routes.

In a 'free field' situation that was available to them on a forced-choice task, the hyperlexic children did not think in terms of semantics, but structured their response on the basis of 'sound'. (Comparative data on normal children will be forthcoming.)

Although there were no significant differences between grossly and mildly altered and nonaltered paragraphs, reading time was consistently longer in the more altered paragraphs. It was also evident from behavioural observations that the majority of the children's reading was disrupted by improperly placed periods. The period, a grammatical device which gives semantic information, had 'meaning' at some level for the hyperlexic children.

The most striking facet of the hyperlexic children's performance on metalinguistic reading tasks was their inability to grasp instructions. More than half the sample could not comprehend the tasks' instructions, much less perform them correctly. While access into the 'cognitive unconscious' is extremely beneficial in the acquisition of reading in normal children (Rozen and Gleitman, 1977), it may not be necessary for learning to read in special instances.

Function words presented no difficulty for the hyperlexic children, despite the fact they have no lexical component (Patterson, 1981) and are irregular in spelling. This may reflect their high frequency.

Routes to Reading Aloud

Three routes to oral production in reading have been proposed (Morton and Patterson, 1980). The first is lexical. The written word is recognized visually, enters the lexicon where its phonology and semantic description are housed, and then its articulation is produced. Dimensions such as frequency and imagery, but not spelling exceptionality, would have impact on accuracy. The second route is nonlexical. The written word is segmented into graphemic units which are then converted into phonemes or phoneme clusters by grapheme-phoneme correspondence rules or by analogy. Thus, it is possible to read pseudowords and is easier to read short rather than long regular words. The third route bypasses the lexicon: after the orthography of a word is recognized, its pronunciation is produced directly. Certainly it is possible to learn the pronunciation of a written word without knowing its meaning. (In fact Case 2, when confronted with the word 'yacht', read it aloud phonetically. When told it was 'yot', he correctly read it on its next presentation. It is unlikely the word was in his lexicon, given its low frequency.) It has been proposed that function words may be processed through routes one, two, or three. In a further effort to elucidate routing patterns in the hyperlexic children, the performances of individuals on selected tests of processing (imagery and frequency, pseudowords, exception words, and function words) are listed in Table 21.

All children read high imagery words better than low imagery words and high frequency words better than low frequency words. Six of the 8 hyperlexic children read exception words with greater than 50 per cent accuracy. As over half the words in the latter corpus were very frequent, the lexical route may again be implicated. All the hyperlexic children were able to read function words with better than 85 per cent accuracy and probably *via* the 'direct' route. More specifically, 2 children displayed a relative inability to use grapheme-phoneme transformation rules in pseudoword reading, and 1 child an absolute inability. Word length also had an effect (long pseudowords having more phonemes). (The degree of abstractness of function words did not have an impact on performance, nor did the difficulties some of the children had in reading pseudowords.)

As noted, imagery had an effect on reading, indicating that a semantic lexicon exists and has a structure. That is, words are represented in the lexicon and have attributes that determine ease of access. Alternately, low imagery words may not be attended. The finding is consistent with the process of reading in normal readers and with deep dyslexics in that processing is occurring at a level below the surface. Frequency also had an important effect on the reading of hyperlexic children. Infrequent words may not enter the lexicon, while frequent words do.

Error analyses indicated that visual paralexias occurred relatively frequently. This implies that errors are constrained by the number of letters in a word, the letters of the initial syllable, and the presence of the incorrect, though probably more frequent, word in the child's output lexicon. Visual errors did not occur in conjunction with any linguistic variable, such as imagery. Instead they appeared to be either due to incomplete visual analysis (Marshall and Newcombe, 1973) in which the letter information of the target word was mismatched to the orthographic entry in the lexicon or to the nonexistence of the target word in the lexicon, which made the choice of a visually similar word a necessity. The trend toward more visual errors in short words may have been due to attempts to access them directly and thus 'short circuit' phonological 'checking' strategies.

'Exception' words, by their very nature, violate orthographic rules. It would therefore be expected that phonological errors would predominate, as probably no visual-orthographic match existed. Indeed, this was found. That those hyperlexic readers who were most successful on the task made more visual errors may have been due to their ability to form associative links between the exception words and other words or parts of words in their lexicon.

The near total absence of semantic paralexias may suggest kinship to the normal reading process. Most errors, however, were inchoate and nonspecific. Corrections or alternative responses were rare, although they could be elicited by requesting the child to repeat his response.

An effect of regularity in grapheme-phoneme correspondence rules was noted in the test involving inconsistently pronounced pairs of words (gown-grown). More than twice as many errors were made on the less regular members of the pairs. However, effects of word frequency qualify the conclusion. When neither member of a pair could be read, both visual and phonological errors were of equal frequency. In the discordant condition, phonological errors dominated.

More directly, the majority of the hyperlexic children were able to read pseudowords relatively well, indicating the use of grapheme-phoneme transcoding. In addition, they had some difficulty reading 'exception' words. (The percentage of 'exception' words read correctly was lower than the percentage of words that had low frequency and low imagery values, but the fact remains that the hyperlexic children were able to read a substantial proportion of the 'exception' words.) Pseudohomophone reading with attendant semantic demands indicated that the hyperlexic children were able to reach the lexicon *via* the phonological route.

Concluding Comments

When interpreting the data it should be recognized that attention and motivation might have had a large effect on the results. While we attempted to encourage maximum effort in the children, the variability in behaviour they displayed cannot be overlooked. (In one instance, correct task behaviour could be elicited only by allowing a subject to 'karate chop', rather than point to the correct visual targets.) Moreover, given the lack of normal controls, the interpretation of the data must remain tentative.

Cobrinik (1982) has advanced the view that pattern recognition is extremely acute in hyperlexic children and in some sense can explain their prowess. The present study shows that hyperlexic children have, without instruction, broken the grapheme-phoneme cipher and are able to employ it in reading to gain lexical access. In addition, words made visually deviant through orientation, case, or linearity manipulations produced little effect on the reading of hyperlexic children, indicating that their visual scheme of orthography is abstract. Only by adding an extraneous symbol (+) between each letter was hyperlexic reading disturbed: a disattention phenomenon is implicated.

How hyperlexic children learn to read cannot be said with certainty. Our historical data indicate that it probably involves lexicon, as the children's first reading responses were made to product wrappers, commercials, billboards, or TV shows and programme guides. At some point, however, they discover the rules of transformation between phonemes and graphemes without instruction. A study is needed to observe a hyperlexic child in the process of learning to read.

Many of the hyperlexic children exhibited extreme difficulties reading paragraphs. One did not respect white space between words, others exhibited attentional difficulties, still others appeared to find the task aversive. It may be that the semantic demands involved in the processing of connected sentences are high and require much cognitive effort. Reading single words that had concrete meaning appeared more reinforcing and seemed to take on a self-stimulatory quality for the hyperlexic children. Those children who had the best comprehension of connected discourse, as assessed by the Token Test, also had metalinguistic awareness and were better able to manage the demands of connected visual language. Two of the children had conversational speech and had higher levels of comprehension. The remaining children read but at no point appeared to use reading as a mode to engage in interpersonal exchanges.

Healy *et al.* (1982) found that hyperlexic children do equally poorly in both the auditory and visual comprehension of language. While we concur with this, it in no way indicates how hyperlexic children, lacking these language and communication skills, come to exercise their linguistic functions in a complex, integrated way without formal instruction. The poor performance of hyperlexic children on Piagetian tasks (Healy *et al.*, 1982) requiring high degrees of conceptual and mental manipulative abilities is mirrored in the performance of the hyperlexic children in the present study on metalinguistic tasks which entail the notion that language can be objectified.

The reading of hyperlexic children is akin to children just beginning to move from 'beginning reading' to 'skilled reading'. Evidence for this is based not only upon grade level but upon error analysis. It has been shown for normal children there is increasing sensitivity and attention to the graphemic display (Biemiller, 1970). However, the hyperlexic children do not integrate a second strategy based upon meaning and grammaticality within sentences.

Reading is a higher order cognitive skill. It involves attention, memory, bimodal integration, knowledge that linguistic information can be represented either phonetically or graphically, awareness of phonological segments, the ability to fuse units, awareness of orthographic structure within words, and the abstraction of invariant patterns over many contexts through comparison with contrasting patterns (thus leading to generalization), motivation and reinforcement, visual perception, auditory perception, and articulatory skills. The abilities observed in the sample under discussion pose difficulties for those cognitive psychologists of language who believe that metalinguistic awareness is necessary in learning to read and for reading readiness theorists who believe that certain skills (e.g. visual-motor, body schema) are necessary before reading can emerge.

Also, it has been shown in normal adults that reading aloud involves activation of discrete areas of brain, including the visual cortex, the frontal eye fields, Broca's area, the supplementary motor cortex, the sensorimotor mouth area, and auditory cortex (Lassen *et al.*, 1978). Luria (1966) also suggested that reading involves a 'dynamic mosaic of cortical zones' involving perception, phonetic analysis and synthesis, serial selection, and articulation (as well as acoustic gnosis). Historical information, including pre- and perinatal risk factors, neurological examination, and grossly delayed language systems, indicated that all children in the sample suffered from brain dysfunction that was both severe and chronic. How reading can occur in such a context thus warrants further neurological investigation (e.g., rCBF studies, PET scanning).

Hyperlexic children do process semantically during reading and have a lexicon. However, the lexicon is rather limited, concrete and often cannot be easily manipulated in a metalinguistic sense.

Though the children appear to lack many of the cognitive component-skills thought necessary for reading, neither are their remaining abilities hypertrophied. Thus, if the 'skeletal' or hermetic process by which they learn to read can be delineated, it may be possible to use this knowledge to design instructional programmes for those more normal children encountering difficulties in learning to read.

ACKNOWLEDGEMENTS

We wish to thank Dr Frances Eldis, Dr Joseph Fischhoff, Ms Leslie Green, Dr Andrew Maltz, Dr Arthur Robin, and Ms Judith Uznis for permission to assess their patients. The investigation was supported by grants from the Wayne State University Faculty Research Award Program and the W. T. Grant Foundation to the first author.

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(*Received June 9, 1983. Revised December 20, 1983*)

APPENDIX

TABLE 1 PERFORMANCE ON WECHSLER AND 'PIAT' VARIABLES

Var	*Perfect score*	$\bar{X}$	*SD*	*Min*	*Max*	*Kurt*	*Skew*
VR		12 125	11 692	0.0	25 0	−1 999	0 148
VSS	19	4 500	3 891	1 0	10 0	−1 963	0 504
DSR		6 875	3 227	2 0	12 0	−0 141	−0 157
DSSS	19	5 625	2 387	1 0	9 0	1 457	−0 837
BDR		15 625	16 017	0 0	44 0	−0 299	0 953
BDSS	19	7 250	4 268	1 0	12 0	−1 763	−0 215
CDR		20 625	7 230	9 0	29 0	−1 113	−0 359
CDSS	19	4 125	2 031	1 0	7 0	−0 886	−0 224
PIATRRP	100	62 500	36 277	7 0	100 0	−1 444	−0 444
PIATRRG		4 662	1 243	2 8	6 4	−0 736	−0 150
PIATRCP	100	40 500	40 267	3 0	99 0	−1 471	0 602
PIATRCG		3 337	1 944	1 9	7 2	1 146	1 418
PIATSPLP	100	50 500	37.664	2 0	100 0	−1.628	0 289
PIATSPLG		4 025	1 425	2 4	6 2	−1.502	0 393
PIATMP	100	4 500	6 663	1 0	19 0	3.230	1 946
PIATMG		1 100	1 346	0 100	3 400	−1 082	0 887

TABLE 2 PERFORMANCE ON READING NUMBERS AND FUNCTION WORDS

Var	*No of items*	$\bar{X}$	*SD*	*Min*	*Max*
Number	20	18 750	3 151	11 0	20 0
Function	46	42 625	7 596	24 0	46 0

TABLE 3 PERFORMANCE ON READING WORDS OF VARYING FREQUENCY AND IMAGERY

Var	*No of items*	$\bar{X}$	*SD*	*Min*	*Max*
HFHI	25	21 625	4 307	12 0	25 0
HFLI	25	19 000	7 010	3 0	25 0
LFHI	25	20 250	5 751	7 0	25 0
LFLI	25	15 125	6 357	3.0	21 0

TABLE 4 TWO-WAY 'ANOVA' OF PERFORMANCE ON READING WORDS OF VARYING FREQUENCY AND IMAGERY

Factor	*SSQ*	*df*	$\bar{X}$ *SQ*	*F*	*P*
Frequency	55 125	1	55 125	23 56	0 0018
Error	16 375	7	2 339		
Imagery	120 125	1	120 125	29 63	0 0010
Error	28 375	7	4 059		
Interaction	12 500	1	12 500	2 03	0 1968
Error	43 000	7	6 143		

TABLE 5 ERROR ANALYSIS OF WORDS OF VARYING FREQUENCY AND IMAGERY

Error	*HFHI*	*HFLI*	*LFHI*	*LFLI*
Visual	3 (21%)	8 (29%)	4 (26%)	20 (32%)
Phonological	3 (21%)	3 (9%)	3 (20%)	6 (10%)
Derivation	0 (0%)	3 (9%)	0 (0%)	1 (2%)
Other	8 (58%)	22 (53%)	8 (54%)	35 (56%)
Total	14	33	15	62

TABLE 6 PERFORMANCE ON SHORT AND LONG WORDS AND PSEUDOWORDS

Var	*No of items*	$\bar{X}$	*SD*	*Min*	*Max*	*t-value*	*P*
WDS	(25)	22 000	4 356	11 0	25 0	−3 04	0 019
WDL	(25)	18 500	6 256	6 0	25 0		
PWS	(25)	15 750	7 979	0 0	25 0	−3 43	0 11
PWL	(25)	11 750	8 172	0 0	24 0		

TABLE 7 PERFORMANCE ON READING AND SPELLING RECOGNITION OF PSEUDOWORDS

Var	*No of items*	$\bar{X}$	*SD*	*Min*	*Max*
PWSPEL	12	8 125	1 885	4 0	10 0
PWREAD*	12	9 33	0 577	9 0	10 0

* n = 3

TABLE 8 PERFORMANCE ON READING WORDS OF VARYING REGULARITY

	$\bar{X}$	*SD*	*Min*	*Max*
Inconsistent pairs (No correct) (Max = 20)	10 750	4 334	7 0	18 0
Inconsistent pairs (No pairs concord correct) (Max 10)	3 0	3 1622	1 0	9 0
Exception words (No items = 25)	14 625	4 507	6 0	22 0

TABLE 9 PERFORMANCE ON TASKS ASSESSING COMPREHENSION

Var	*No of items*	$\bar{X}$	*SD*	*Min*	*Max*	*Kurt*	*Skew*
Token	16	7 375	5 069	2 0	14 0	−1 938	0 550
PPVT	35	25 331	1 840	17 0	35 0	−1.523	0 227
PPVTPHP	35	21 175	2 989	2 0	32 0	0 193	−0 914
PPVTPHP-RW DIF	%	45 250	2 547	17.0	100 0	2 610	1 446
DRRLCOMP	%	33 875	37 369	0 0	86 0	−1 544	0 633
Forced-choice							
Visual		3 500	2 268	1 0	7 0	−1 303	0 049
Semantic		4 875	3.603	0 0	9 0	−1 964	−0 452
Auditory		11 625	4 955	6 0	18 0	−1 707	0 233

TABLE 10 PERFORMANCE ON TASKS ASSESSING METALINGUISTIC PROCESSING

Var	*No of items*		$\bar{X}$	*SD*	*Min*	*Max*
LEXDEC*	50	(Overall)	45.667	2.517	43.0	48.0
	12	LIWD	9.667	0.577	9.0	10.0
	13	HIWD	13.0	0.0	13.0	13.0
	25	PWD	23.0	2.517	20.0	25.0
PHONSN*	5	SS	2.150	2.217	0.9	5.0
	5	SD	3.250	2.363	0.0	5.0
	5	DS	0.250	0.500	0.0	1.0
	5	DD	5.00	0.0	5.0	5.0

* n = 3.

TABLE 11 PERFORMANCE ON TASKS IN WHICH READING WAS EXPERIMENTALLY 'DISTURBED'

*Task**†	$\bar{X}$	*SD*	*Min*	*Max*
Alt Par (T1, ¶1)	12.167	5.529	7.0	28.0
Alt Par (T1, ¶2)	22.167	10.304	10.0	37.0
Par (T2, ¶1)	7.833	3.817	5.0	15.0
Par (T2, ¶2)	14.833	8.183	7.0	30.0
Alt Par (T3, ¶1)	11.5	6.834	4.0	23.0
Alt Par (T3, ¶2)	27.0	26.751	11.0	50.0

* n = 6 † Score in seconds

Task	*No of items*				
VDW C	6	4.575	1.356	2.0	6.0
O	6	5.250	1.035	3.0	6.0
+	6	2.0	1.512	0.0	4.0
L	6	5.250	1.389	2.0	6.0
S	6	4.625	1.408	2.0	6.0
VDW Total	30	22.00	5.182	10.0	27.0

TABLE 12 CORRELATIONS BETWEEN AGE AND SELECTED COGNITIVE AND ACHIEVEMENT VARIABLES

	Age		*Age*
VR	0.5897	PIATRRG	0.6607
Sig	0.062	Sig	0.037
VSS	0.2078	PIATRRP	−0.9639
Sig	0.311	Sig	0.000
DSR	0.2155	PIATRCG	0.8167
Sig	0.304	Sig	0.007
DSS	0.1080	PIATRCP	−0.7314
Sig	−0.400	Sig	0.020
BDR	0.1912	PIATMG	0.6267
Sig	0.325	Sig	0.048
BDSS	−0.0866	PIATMP	−0.2089
Sig	0.419	Sig	0.310
COR	0.6818	Token	0.7877
Sig	0.031	Sig	0.010
COSS	−0.4794		
Sig	0.115		

TABLE 13 CORRELATIONS AMONG WECHSLER VARIABLES

	VSS	*DSSS*	*BDSS*	*COSS*
VSS		0.3827	0.4969	0.5032
Sig		0.175	0.105	0.102
DSSS			0.4479	0.2364
Sig			0.133	0.287
BDSS				−0.0183
Sig				0.483

TABLE 14 CORRELATIONS BETWEEN 'WISC-R' SUBTESTS AND ACHIEVEMENT AND READING TASKS

	PIATRRG	*PIATRCG*	*PIATMG*	*Func*	*HFHI*	*HFLI*	*LFHI*	*LFLI*	*VDW(TOT)*	*Excep*
VSS	−0.4148	0.5750	0.5589	−0.3795	−0.0370	−0.0245	0.1104	0.2440	−0.1384	0.0123
Sig	0.153	0.068	0.075	0.177	0.465	0.477	0.397	0.280	0.372	0.488
DSS	−0.1928	−0.1729	−0.1220	−0.2068	0.4695	−0.5455	−0.1212	−0.1807	−0.3230	−0.5576
Sig	0.324	0.341	0.387	0.307	0.120	0.081	0.387	0.334	0.218	0.076
BDSS	−0.4001	0.1739	0.4444	0.0130	−0.1288	−0.1342	−0.0854	−0.2546	−0.5875	−0.2256
Sig	0.163	0.340	0.135	0.488	0.381	0.376	0.420	0.271	0.063	0.296
COSS	−0.4910	−0.1718	−0.0638	−0.8158	−0.4849	−0.3976	−0.2651	−0.5988	0.2223	−0.3675
Sig	0.108	0.342	0.440	0.007	0.112	0.165	0.263	0.058	0.298	0.185

TABLE 15 CORRELATIONS AMONG 'PIAT' VARIABLES

	PIATRRG	*PIATRCG*	*PIATSPG*	*PIATMG*
PIATRRG		0.3416	0.7904	0.2917
Sig		0.204	0.010	0.242
PIATRCG			0.7163	0.9098
Sig			0.019	0.001
PIATSPG				0.7401
Sig				0.018

TABLE 16. CORRELATIONS BETWEEN 'PIAT' AND SELECTED READING TASKS

	Func	*HFHI*	*HFLI*	*LFHI*	*LFLI*	*VDW(TOT)*	*Excep*	*PWL*	*PWS*	*WL*	*SW*
PIATRRG	−0.6641	0.7350	0.7186	0.8144	0.7857	0.1964	0.6467	0.5714	0.6831	0.6108	0.7488
Sig	0.036	0.019	0.022	0.007	0.010	0.321	0.042	0.069	0.031	0.054	0.016
PIATRCG	0.3664	0.7655	0.7609	0.7486	0.4880	0.0629	0.7731	−0.3172	0.1000	0.7118	0.7044
Sig	0.186	0.013	0.014	0.016	0.110	0.441	0.012	0.222	0.407	0.024	0.206
PIATMG	0.4218	0.7702	0.7656	0.7783	0.5073	0.1760	0.7720	−0.2537	−0.0520	0.7018	0.7586
Sig	0.149	0.013	0.013	0.011	0.100	0.344	0.012	0.272	0.451	0.026	0.015

TABLE 17 CORRELATIONS AMONG VARIABLES CONCERNING WORD LENGTH AND REGULARITY

	Excep	*PWS*	*PWL*	Inconsist *Prs*	*WS*	*WL*
Excep		0.4172	0.2635	0.4097	0.8583	0.8554
Sig		0.152	0.264	0.157	0.003	0.003
PWS			0.9515	0.4939	0.4654	0.3927
Sig			0.001	0.107	0.123	0.68
PWL				0.4097	0.3314	0.2275
Sig				0.157	0.211	0.294
Inconsist PRS					0.8138	0.5818
Sig					0.007	0.065
WS						0.7780
Sig						0.011

TABLE 18 CORRELATIONS BETWEEN TOKEN TEST AND SELECTED COGNITIVE, ACHIEVEMENT, AND READING TASKS

	Token		*Token*
VSS	0.1104	PPVTPHP	0.8434
Sig	0.192	Sig	0.004
DSSS	0.2195	PPVT	0.5543
Sig	0.301	Sig	0.077
BDSS	0.4233	PIATRRG	0.4338
Sig	0.148	Sig	0.141
COSS	−0.3273	PIATRCG	0.7285
Sig	0.214	Sig	0.020
HFHI	0.6768	PIATMG	0.8280
Sig	0.033	Sig	0.006
HFLI	0.6000	DRRLCOMP	0.6771
Sig	0.056	Sig	0.033
LFHI	0.7758		
Sig	0.012		
LFLI	0.6386		
Sig	0.044		
Func	0.6850		
Sig	0.030		

TABLE 19 RELATIONSHIP BETWEEN TOKEN TEST PERFORMANCE (ABOVE OR BELOW THE MEAN OF 7.35) AND METALINGUISTIC AWARENESS (CAPACITY TO PERFORM ON BOTH THE LEXICAL DECISION AND PHONOLOGIC SOUNDS TASKS)

		Metalinguistic awareness	
		Perform	*Cannot perform*
Token	High ($> \bar{X}$)	3	0
	Low ($< \bar{X}$)	0	5

TABLE 20 CORRELATIONS AMONG TASKS ASSESSING COMPREHENSION

	PPVTPHP	*PPVT*	*PIATRC*	*DURRLCOMP*
PPVTPHP		0.3333	0.8539	0.6261
Sig		0.210	0.003	0.048
PPVT			0.3660	0.0368
Sig			0.186	0.466
PIATRC				0.6667
Sig				0.035

TABLE 21 PERFORMANCES OF INDIVIDUAL HYPERLEXIC CHILDREN

Patient	*Imag (High/Low)* *No of items = 50/50*	*Freq (High/Low)* *No of items = 50/50*	*Excep Words* *No of items = 25*	*Func* *No of items = 46*	*PW (Short/Long)* *No of items = 25/25*
C R	46/38	47/37	17	45	9/4*
C K	40/35	39/36	13	46	20/16
T M	48/42	46/44	15	46	17/16
L N	41/26	38/29	11*	43	21/11
A S	45/44	50/43	18	46	25/24
D S	19/6*	15/10*	6*	40	0/0*
D M	42/37	43/38	15	42	21/11
M H	50/45	49/46	22	46	15/11

* Accuracy ≤ 50 per cent

Brain (1984), **107**, 787-809

ANALYSIS OF CEREBELLAR MOTOR DISORDERS BY VISUALLY GUIDED ELBOW TRACKING MOVEMENT

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SUMMARY

Motor control was analysed by a visuomotor tracking movement using elbow flexion both in patients with cerebellar ataxia and in normal controls. A TV screen was divided into upper and lower halves, in each of which a vertical strip was displayed. The upper strip (T, target) was moved horizontally from the centre of the screen to the left or right by ramp voltage. The lower strip (D, displacement of the handle) was moved in proportion to angular displacement of the handle by a potentiometer coupled to the handle axis. The subject, while sitting in front of the TV screen, had to make D match the movement of T by controlling the handle with his right arm. The range of T movement was 30 deg in terms of the handle's angular movement. T velocity was 7.5, 15 or 30 deg/s. The subjects were told the direction and velocity of T in advance. The process of tracking was divided into three phases (initial catch-up phase, middle pursuit phase, and terminal phase), in each of which the performance of cerebellar ataxia patients differed from that of the controls. The characteristic features of the ataxic cases were (1) prolongation of the reaction time, mainly due to the increase of premotor time; (2) difficulty in selecting an appropriate amplitude of initial peak velocity in proportion to the target velocity in the inital catch-up phase; (3) disruption of smooth continuous movement, namely, the saccadic pattern in the middle pursuit phase; (4) delay in the initiation of deceleration in the terminal phase; (5) difficulty in corrective adjustment in reaching the final target point; and (6) irregular EMG activity in the agonist muscles and/or cocontraction of the antagonistic muscles. Quantitative treatment of the second and third features, as exemplified in the relationship between initial error and initial peak velocity and in the ratio of the movement arrest period, respectively, was found to be helpful in the evaluation of disease severity. The significance of these findings is discussed and the role of the cerebellar system in the control of slow voluntary movement is stressed.

INTRODUCTION

Recent neurophysiological studies on cerebellar function in behaving animals have yielded substantial advances. They have shown that the cerebellum not only plays a critical role in initiation but also in the overall performance of voluntary movement (*see* Thach, 1970; Brooks, 1974; Meyer-Lohman *et al.*, 1977; Lammarre

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and Jacks, 1978; Stein, 1978; Mano and Yamamoto, 1980; Vilis and Hore, 1980; Sasaki *et al.*, 1982; *see also* Brooks and Thach, 1981). Most of these studies, however, deal with ballistic or rapid movements which would be categorized as step-mode movements, thus revealing the importance of the cerebellum in open-loop control of movement (*see* Kornhuber, 1971; Ito, 1972). In step-mode movements, completed in one action, the subject has only to select and execute a set of preprogrammed motor commands. Although kinaesthetic information from the motor organs concerned would be generated by the movement and fed back to the CNS, it is generally assumed that their central action, reflexly or *via* higher structures, on the overall control of the movement is negligible. This is due either to the brevity of performance or because the information has already been incorporated in the program through experience gained from preceding trials (*see* Miles and Evarts 1979).

In our daily tasks, however, we are often required to make slow and accurate movements which are also affected in cerebellar ataxia. Although some investigators have stated that slow movements are less affected by cerebellar dysfunction (Kornhuber, 1971; Hallet *et al.*, 1975*b*; Brooks, 1979), recent studies both on eye and limb movements in the monkey suggest the importance of the cerebellum in controlling slow as well as rapid movements (Lisberger and Fuchs, 1978; Stein, 1978; Mano and Yamamoto, 1980). The present study was designed to elucidate a cerebellar role in the development of motor programs for slow and accurate movements by particularly exacting standards for the quantitative evaluation of the skills in normal subjects and in patients with cerebellar ataxia. For this purpose, we studied the actual pattern of elbow movement by adopting a ramp-mode visually guided tracking task. In this paper, we will describe the fundamental features of the tracking pattern both in normal controls and in patients with cerebellar ataxia. Part of this study has been published elsewhere (Beppu *et al.*, 1983).

METHODS

Subjects

Fifteen patients with cerebellar ataxia (6 females and 9 males, aged 30 to 65 yrs) and 14 normal healthy controls (3 females and 11 males, aged 23 to 67 yrs) were studied. All subjects were informed of the purpose and procedures of the experiment in advance, and gave informed consent. The clinical data for the patients are summarized in Table 1. All except 2 suffered from cerebellar or spinocerebellar degeneration, categorized according to the classification of Greenfield (1954). At rest, these patients showed no sign of tremor. One case of spinocerebellar degeneration showed slight muscle weakness, 2 a mild disturbance of deep or superficial sensation, and 3 slight rigidity in the extremities. None of these symptoms was severe enough to incapacitate patients for the present tracking task. The 2 additional ataxic patients were a case of hypoxic cerebellar damage and a case of cerebellar ataxia due to the sequelae of acute lithium intoxication. They had recovered fully except for cerebellar deficits that were present at the time of examination. Pneumoencephalography in the former patient and computed tomography in the latter revealed prominent cerebellar atrophy. The patients were classified into three groups (A, B, and C) according to the clinical severity, or activities of daily living (ADL). Group A consisted of cases with mild disability who were capable of leading a normal life for

TABLE 1. CLINICAL DATA FOR PATIENTS WITH CEREBELLAR ATAXIA

						Tendon reflexes			*Ataxia*			
ADL	*Case*	*Age, Sex*	*Duration of illness (yrs)*	*Diagnosis*	*Muscle tone*	*UL*	*LL*	*Pathological reflexes*	*UL*	*LL*	*Nystagmus*	*Sensory disturbance*
A	M S	57, M	3	Cerebellar	↓	+	+	—	+	+	—	—
	R F	49, M	9	Spinocerebellar*	↓	+	+	+	+	+	Horizontal	+ (superficial)
	K N	45, M	7	Cerebellar	↓	+ +	+ +	—	+	+	Horizontal	—
	T I	37, M	4	Spinocerebellar*	↓	±	±	—	+	+	—	—
	S T	30, M	5	Cerebellar*	↓	+	+ + +	—	+	+	Horizontal	—
B	T F	65, M	2	Spinocerebellar	↓	+	+	—	+	+ +	—	—
	S A	64, M	3	Cerebellar	↓	+	+	—	+	+	—	—
	M T	63, F	1	Cerebellar*	↓	+ +	+ +	—	+	+	—	—
	S I	60, M	2	Spinocerebellar	↑ (R)	+	+	—	+	+	—	—
	F T	57, F	2	Spinocerebellar	↓	+ + +	+	—	+	+ +	Horizontal	—
	K N	56, F	10	Spinocerebellar*	↓	+	+	+	+	+ +	Horizontal	—
C	M N	48, F	2	Spinocerebellar	↑ (RS)	+ +	+ +	+	+ +	+ +	Horizontal	—
	K N	27, F	12	Spinocerebellar*	↑ (RS)	+ + +	+ + +	+	+ +	+ +	—	+ (deep)
	Y K	54, M	1	Lithium intoxication	↓	+	+	—	+	+ +	—	—
	A M	26, F	10	Anoxic cerebellar damage vertical	N	+	+	—	+ +	+ +	Horizontal and vertical	—

ADL = activity in daily living Subtypes of cerebellar and spinocerebellar degeneration follow the classification of Greenfield (1954), * = hereditary cases, R = rigid, RS = rigidospastic, UL and LL = upper and lower limbs, normal range for tendon reflexes = +-++

themselves; group B included cases of moderate severity who had had to give up their jobs but could still carry out other daily activities; group C comprised severe cases who could not care for themselves.

All the patients fully understood the present tracking task when explained before the tests and were cooperative during the examination.

Apparatus and Methods

The arrangement of the examination system is shown in fig. 1. The principle of the display system for instruction of the tracking movement was the same as that used by Mano and Yamamoto (1980).

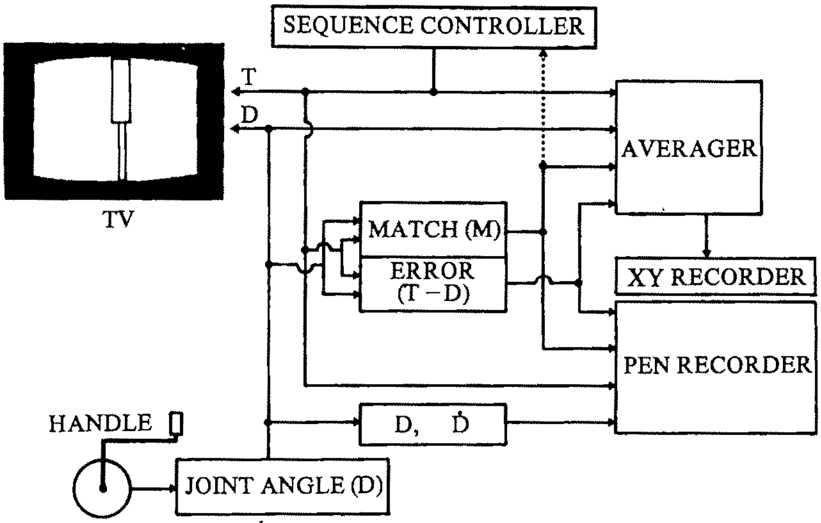

FIG. 1 Schematic illustration of experimental arrangements.

A 20 inch colour TV screen (Sony, KV-2077) was used for the display. The screen was divided into upper and lower halves, each of which displayed a vertical strip. The upper strip (target, T), 33 mm wide, was moved at a constant velocity to the right or left from the centre of the screen by a ramp voltage. The lower strip (control cursor, D), 11 mm wide, was moved in proportion to the angular displacement of the handle by a potentiometer coupled to the axis of the handle. A ratio of 3 : 1 for the width of the cursor strips was chosen for the convenience of the patients. A narrower target is naturally better for evaluation of accuracy, but too narrow a target imposed excessive stress on the ataxic patients. The present ratio was a compromise after a few preliminary experiments had been performed.

The handle was made from a metal frame and adapted for elbow flexion-extension movement in a horizontal plane. The length of its arm could be adjusted to that of the subject's forearm and the axis was supported by a ball-bearing system to minimize frictional resistance.

The principle of the tracking task for the subject is to make the cursor follow the moving target while keeping it in the centre of the target strip with elbow flexion movement. The subject sat squarely in front of the TV screen, at a distance of 130 cm from the screen. The arm, usually the right for right-handed subjects and the left for left-handed subjects, was abducted approximately 90 deg at the shoulder, and the forearm was supinated allowing the biceps and brachialis muscles to become the prime flexors of the elbow. The starting angle of the elbow joint was 90 deg. The range of the target movement was 30 deg. and the velocity varied between 7.5, 15 and 30 deg/s in terms of the handle's angular displacement. The handle was movable in both flexion and extension by 35 deg at the maximum, which occurred when the control cursor reached the lateral end of the screen. In keeping the target range at 30 deg, this additional 5 deg of handle movement allowed for any hypermetric reaction. In preliminary experiments extension movements were also tested. Since there was no substantial difference from the flexion experiment, flexion movements were mainly studied.

The experiment began after instruction and demonstration of the task to the subject by the experimenter. Experimental sequences were controlled by a microcomputer system (TRS-80, model I), which was modified by the demands of the present study. The system was activated when the subject matched the control cursor to the target in the centre of the display. After the subject held the control cursor in the centre for a few seconds, an acoustic warning signal (1 KHz, 0.8 s) was given. Then, after an unpredictable foreperiod ranging between 1.3 and 3.8 s separated in 0.5 s intervals, the target started to move in either direction. The subject was usually informed of the direction and velocity of the target movement in advance. After the completion of tracking and holding the control cursor within the target zone at the lateral end of the display for 2 s, the target automatically returned to the initial centre position. The next trial began when the subject brought the control cursor into the target zone. Thus the subject could begin the task whenever he wished. This latter feature, as well as the warning signal, was necessary for keeping the subject alert during the task. During one session, 12 trials were repeated in which the velocity of the target movement was fixed. In an average experiment, two sessions for each target velocity, that is six sessions (72 trials in total) were recorded. The intervals between each trial, partly decided by the subject as described above, ranged on average from 14 to 20 s. Data for analysis were obtained after the subject had practised the task movement several times.

The recording system is also illustrated in fig. 1. Parameters relevant to the movement such as target signal (T), handle trajectory (D), velocity ($\dot{D}$), and error (T – D) were recorded in parallel on an 8 channel data recorder (Sony, DFR-3915) and an 8 channel recticorder (Watanabe Sokki, WTR-331-8L). Electromyographic activity of the elbow flexor and extensor muscles (biceps brachii, brachialis and triceps brachii) were recorded routinely by implanted wire electrodes (0.09 mm, insulated except for about 5 mm at the tip). In a few cases surface electrodes were also used.

RESULTS

Typical records of the tracking movement by the elbow from a normal subject are shown in fig. 2. The present task of ramp-mode tracking has three contrasting features: the starting action, the movement with constant velocity, and the stopping movement. According to these differences in strategy of movement, we divided the whole process of visuomotor tracking movement in normal subjects into three phases: the *initial* catch-up phase (I-phase), the *middle* pursuit phase (M-phase) and the *terminal* arrest phase (T-phase). The characteristics of motion patterns in each phase were well demonstrated in the traces of the error (*T-D*) and the handle velocity ($\dot{D}$), particularly during the slowest tracking trials (fig. 2A). In the I-phase, with a delay of several hundred milliseconds to the target start (reaction time), the subject moved the handle quickly and caught up accurately with the preceding target. The velocity ($\dot{D}$) trace developed quickly, attaining a peak after a few hundred milliseconds. It then declined towards the level of target velocity for transition to the M-phase. The first peak of the $\dot{D}$ trace, which will subsequently be termed the initial peak velocity (IPV), may represent the catch-up reaction to a foregoing target. In the M-phase, which is defined as the period from the end of initial peak to the beginning of the deceleration for arrest, the normal subjects moved the handle in a fairly constant velocity matching it to the target velocity. By doing this, they were able to keep the control cursor within the target zone. Some irregular undulations for minor adjustment were observed. The T-phase was the period of deceleration and final arrest of the handle in response to the target arrest.

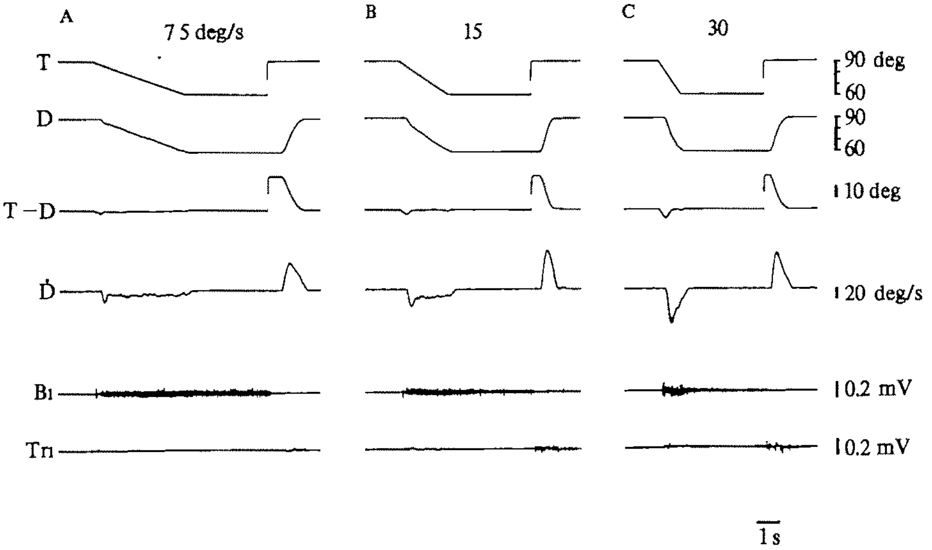

FIG. 2 Specimen records of the tracking elbow flexion movement in a normal subject. T, D, T−D and $\dot{D}$ = target, handle displacement, error, and handle velocity, respectively Bi = biceps, Tri = triceps.

The deceleration often started a few hundred milliseconds before the target arrest causing a lag, which may have indicated some anticipatory process.

The basic pattern of motion described above remained qualitatively the same when the target velocity increased (fig. 2B and C). The amplitudes of IPV and pursuit velocity increased, but the duration of the M-phase was shortened. In many trials in which a target velocity of 30 deg/s was tested the M-phase was so short that it went almost unnoticed. This created the effect that the T-phase immediately followed the I-phase (fig. 2C).

This present task was so easy for healthy subjects that all controls achieved the above tracking pattern after a few trials and subsequently maintained it. Repeated training sessions did not make substantial changes in the results. On the other hand, the tracking pattern in patients with cerebellar ataxia was quite different from the normal subjects (fig. 3). The reaction time was generally delayed and varied widely. The amplitude of IPV was different during each trial and, subsequently, the initial catch-up reaction became less accurate. A smooth transition to the M-phase was lost and, in the M-phase, the Ḋ traces showed a marked saccadic pattern, which formed a striking contrast with the smooth continuous one of normal subjects. In the T-phase, they showed some difficulty in accurate deceleration and stopping, and were liable both to overshoot or undershoot. The tracking pattern was unstable and varied at each trial during the same session. Since there was no qualitative difference in the tracking movement pattern between the various types of cerebellar disorder, they were classified by their ADL grading.

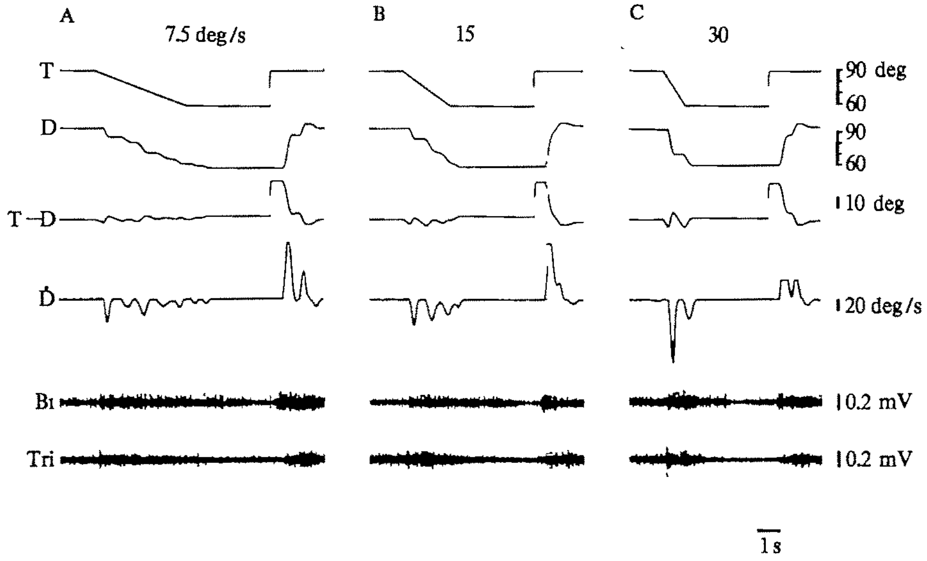

FIG. 3. Specimen records of the tracking flexion movement in a patient with cerebellar ataxia (*Case T.F* in B group, Table 1). Similar illustration to fig. 2.

We have prepared the following quantitative analysis in the I, M and T-phases, respectively, to elucidate the difference in tracking pattern between normal and ataxic subjects on the basis of these general features.

Reaction Time

The reaction time was measured from the polygraph records of each trial. Mean values of reaction time in normal subjects ranged between 210 and 390 ms (open circles in fig. 4A). It was noted that the reaction time shortened as the target velocity increased. The mean values of the mean reaction time for all the control subjects

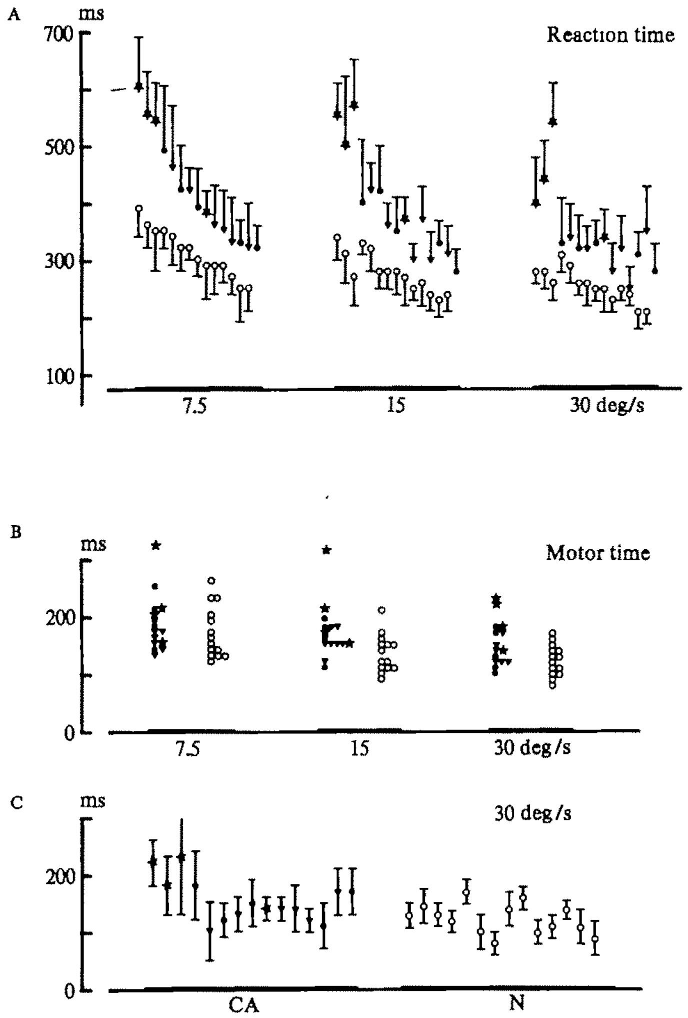

FIG. 4. Reaction times (A) and motor times (B, C) from all control subjects (open circles) and patients with cerebellar ataxia (filled circles = mild, filled triangles = moderate, and asterisks = severe cases). Except in B, they were arranged according to the size of the reaction time in the session of target velocity with 7.5 deg/s. C is a replot of data of B in a 30 deg/s session. CA = cerebellar ataxia patients. N = normal group.

(n = 14) at target velocities of 7.5, 15 and 30 deg/s were 312 (SD = ± 42), 279 (± 35) and 256 (± 28) ms, respectively. This shortening tendency in reaction time was recognized in all the normal subjects without exception, although the times varied. The reaction time of the slowest target velocity differed significantly from that of fastest (student's t-test, two-tailed: $P < 0.05$).

In patients with cerebellar disorders (filled symbols in fig. 4A), the reaction times were longer and showed greater variation than those of the control group. The mean reaction times for all patients for each target velocity were 417 (± 92), 389 (± 90) and 343 (± 71) ms, respectively, and significantly longer than the corresponding control values ($P < 0.05$). Although reaction time in these cases overlapped considerably with that of the controls at the slowest session, the distinction became clearer at the faster target sessions. The delays were most prominent in the severe patients (asterisks in the figure). Those in the mild (circles) and moderate (triangles) cases did not differ between them but were significantly slower than the normal value. There was no significant difference between groups with and without nystagmus, nor between the cerebellar and spinocerebellar cases. The shortening of reaction time with an increase of target velocity was also observed in many ataxic subjects. However, this shortening was not always observed and was not as clearly marked as in the control group.

The reaction time can be divided into two parts: the premotor time and the motor time (*see* Botwinick and Thompson, 1966). The former is the period from the start of the target to the appearance of EMG activity in the agonist muscles (brachialis and biceps brachii). This may be regarded as the time required mainly for processing in the CNS. The latter period is from the appearance of EMG activity to the start of the handle. This value includes times consumed for muscular excitation-contraction coupling and for transmission of muscle contraction to load (handle) movement. Fig. 4B shows that, in the motor time, the above mentioned tendencies, that is, shortening as the target velocity increased and a greater amount of time required on the part of the patients than the control group, were present but in much lesser degree. The difference in the motor time between cerebellar ataxia patients and control subjects was not clear in the trials with a target velocity of 7.5 deg/s but became significant in the trials when the target velocity was increased to 15 and 30 deg/s ($P < 0.05$; fig. 4B and C). The severe cases (asterisks) accounted for the most of the motor time delay and, if these data were omitted, the difference became insignificant. The delay in reaction time in the cerebellar ataxia cases was therefore mainly found to be in the premotor time.

Initial Peak Velocity

As shown in fig. 2, the size of IPVs in normal subjects increased with target velocity and seemed highly relevant to the precise catch-up reaction. We presume for the moment that the subject has already preprogrammed the size of motor outputs for the catch-up response at the initiation of response by foreseeing the error size to be covered. We therefore defined the *initial error*, the target position at the onset of handle movement, for the first approximation of such a predictive error. Its size would be obtained by a function of the test target velocity and reaction time. IPV amplitudes were then plotted against it (fig. 5A). The graph showed a highly linear relationship with a steep regression line (slope = 7.7) which converged towards the original point (*Y*-intercept = 2.3) and had a very high correlation coefficient value ($r = 0.95$).

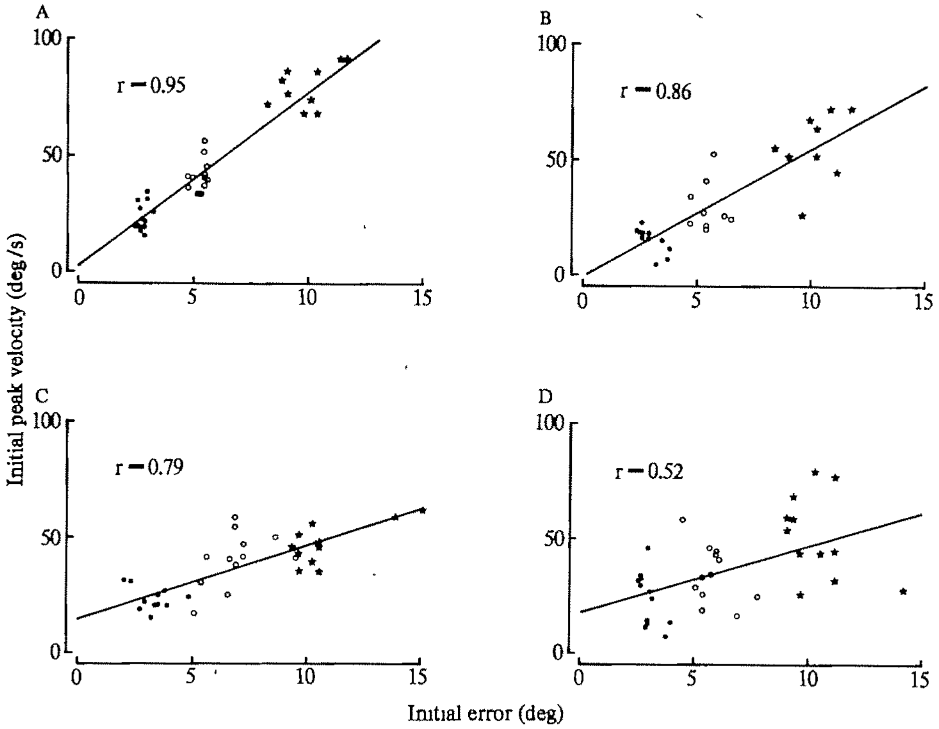

FIG 5. Four examples of scatter diagrams of IPVs (ordinates) against initial error (abscissae). A, normal. B, mild case. C, moderate case D, severe case. Filled circles, open circles and asterisks show the results from the sessions with the target velocities of 7.5, 15 and 30 deg/s, respectively. Regression lines and correlation coefficients are also shown.

Since the IPV plots were obtained from three different conditions (target velocities of 7.5, 15, and 30 deg/s), it might be claimed that it is not justified to calculate regression lines from data of these heterogeneous experiment sessions. However, we think this is not valid for the following reasons. In some control experiments (M. Nagaoka and R. Tanaka, unpublished observations), we also tested at five different target velocities adding 5.5 and 22.5 deg/s to the three standard velocities. The IPV plots from these experiments distributed along the same regression line, and the correlation coefficient was kept within the normal range. In other experiments, in which the target was moved at any of three standard velocities in random sequence, the linear relationship between the IPV amplitude and the initial error was preserved.

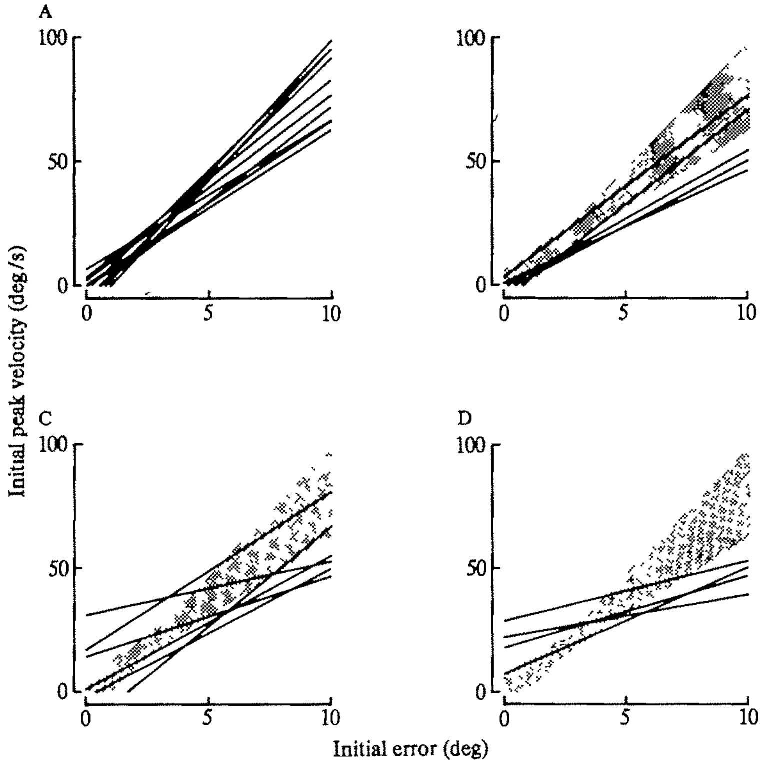

FIG. 6. Superimposed regression lines in each subgroup of subjects. A to D correspond to those in fig. 5. The area occupied by the control subjects (A) is indicated as shaded areas in B, C and D.

Regression lines from all the control subjects are superimposed in fig. 6A. The range of their regression lines distributed in a narrow area. Table 2 shows mean and SD values of slope, Y-intercept and the correlation coefficient, r, of the regression line for the normal subjects.

On the other hand, the size of IPV of the ataxic patients varied in each trial and the linearity between IPV and initial error deteriorated markedly. Three example graphs from mild, moderate and severe subgroups of cerebellar ataxia are presented in fig. 5B, C and D, respectively. Superimposed regression lines from each subgroup are shown in fig. 6B, C and D. In mild cases (figs. 5B and 6B), a gentler slope for the regression lines was noted. This was due to a decrease in IPV sizes at the fastest trial session. Although 2 cases remained in the normal range, their IPV sizes became unstable and the r value fell below the normal range. The values of the slope and r in these cases were significantly different from those of the control (Mann-Whitney U-test, $P < 0.05$). In moderate cases (figs. 5C and 6C), degradation of the slope progressed and, in addition, the Y-intercept tended to deviate positively from the origin. In the severe cases (figs. 5D and 6D), the deterioration further increased.

TABLE 2. MEAN VALUES OF PARAMETERS IN THE REGRESSION LINE FOR INITIAL ERROR-IPV RELATIONSHIPS

	n	*Slope*		*Y-intercept*		*r*	
Normal	14	8.2	(1.7)	−1.8	(4.7)	0.92	(0.02)
Cerebellar ataxia							
Mild	5	6.1	(1.4)	−1.1	(3.3)	0.84	(0.02)
Moderate	6	5.1	(2.1)	7.9	(16.0)	0.79	(0.09)
Severe	4	2.8	(1.1)	19.1	(9.2)	0.61	(0.14)
Total	15	4.8	(2.0)	7.9	(13.3)	0.75	(0.13)

Standard deviations are shown in parentheses.

Although there was some overlap between the neighbouring groups from normal to severe groups, it was clear that deterioration of slope, Y-intercept and r correlated well with the clinical severity (*see also* Table 2).

Pursuit Phase

Throughout the M-phase, the normal subject was able to adjust smoothly and maintain the handle velocity constant with the target velocity. By doing so, the subject matched the handle trajectory to target movement (fig. 2). As shown in the raster velocity records of fig. 7, the movement trajectory of cerebellar ataxia subjects was mostly saccadic throughout the pursuit (*see also* fig. 3). The patient was not able

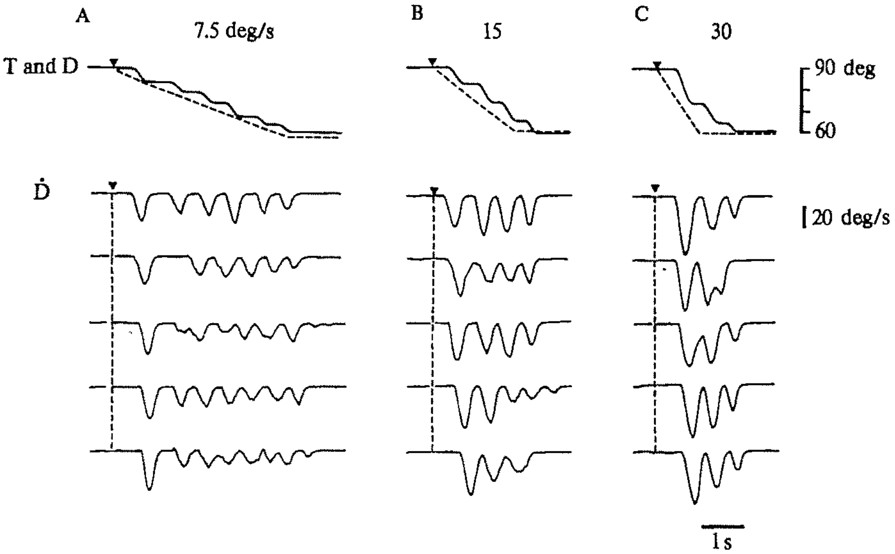

FIG. 7. Raster illustrations of the velocity traces (Ḋ) from a cerebellar ataxia patient (*Case K.N* in c). Start of the target movement is indicated by downward triangles and vertical dotted lines. Traces are realigned according to the reaction times.

to maintain a constant target velocity but repeated a jerky or saccadic movement pattern. The frequency of these jerky movements was distributed between a 1 and 3 Hz range, and showed some irregularity within each trial as well as between different trials. As a result of this, the tracking movement took an irregular staircase pattern, or alternation of catch-up movement and arrest response. The performance was dysmetric, mostly hypometric.

This saccadic pattern does not necessarily indicate a defect in the motor system which may generate a slow continuous movement. When allowed to move at their own chosen speed without target, the patients could move the handle fairly smoothly at any velocity which was used in the present study (compare A and B in fig. 8).

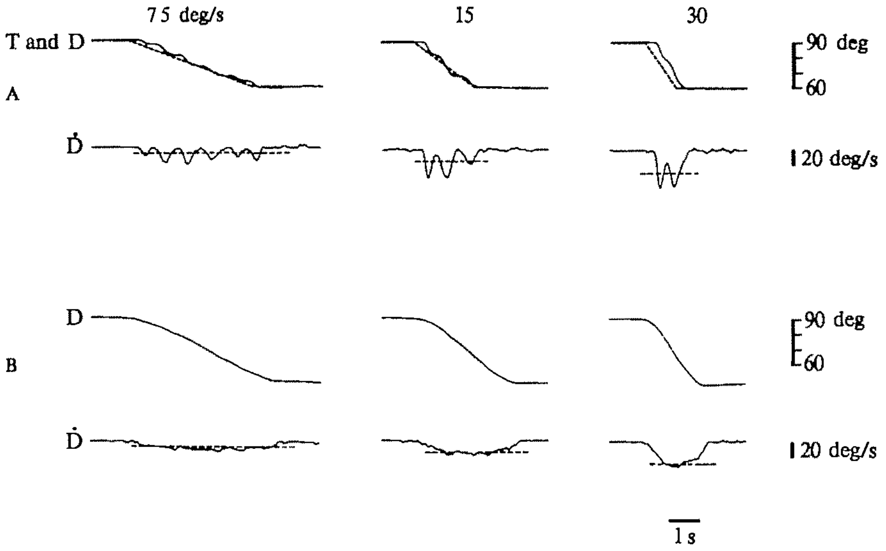

FIG. 8. Different patterns between ramp target tracking (A) and self-paced movements (B) in a cerebellar ataxia patient (an additional case T.S., 47 yrs, F, spinocerebellar type, ADL = group B, no sensory disturbance). Horizontal thin lines in Ḋ traces indicate the velocities corresponding to those given above each column.

To estimate the degree of undulation quantitatively, the ratio of movement arrest period (MAP) to the period of M-phase was calculated. The right-hand figure in fig. 9 shows an example of this MAP ratio calculation. Since it is often difficult to differentiate between the complete movement arrest period and the very slow movement period, the arrest period was defined as the period when the handle velocity decreased below an arbitrarily defined threshold as a percentage of the tested target velocity (the horizontal thick line in the Ḋ trace). Letters A with numbers indicate such periods in sequence. It should be noted that the period of M-phase was measured from its beginning to 0.5 s before target arrest (P in fig. 9).

This was done because the end of the M-phase varied from case to case (*see* next section). In order to discover a more sensitive threshold, we tested various velocity levels, ranging from 10, 20, 40, 60, or 80 per cent of target velocity. The graph in fig. 9 illustrates the MAP ratio calculated from all the normal subjects and from the three subgroups of ataxic patients at the session with a 7.5 deg/s target velocity. It was natural that the MAP ratio increased in all the cases as the threshold level became higher. Nevertheless, there was a significant difference between values of the control group and values of the ataxic subjects at every threshold level. A good correlation was observed between MAP ratio and clinical severity. Calculation with a threshold of 20 per cent of the target velocity seemed to be the most sensitive to differentiate each of three groups of cerebellar ataxia with different severity and normal controls. Trials at faster target velocities were omitted because the duration of the M-phase was short. This reduced the number of saccades, making the MAP ratio less conspicuous.

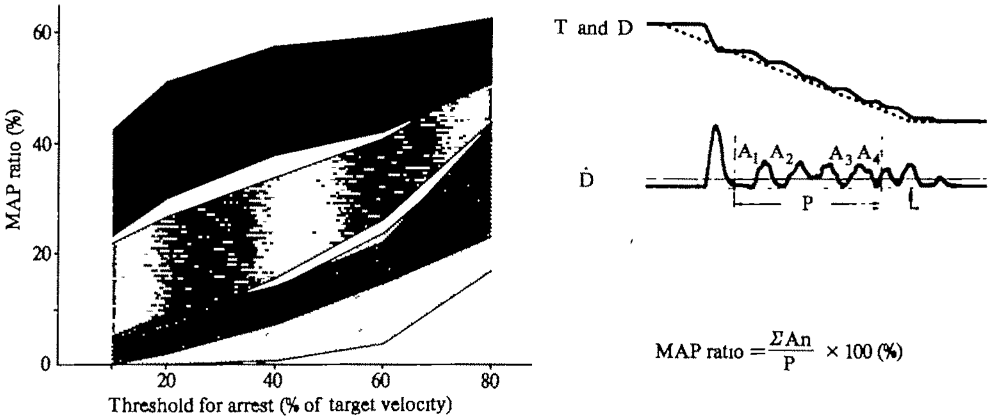

FIG. 9. Ratios of MAP (movement arrest period) are shown against various threshold levels of velocity (abscissae, *see text*). From down to up: normal, mild, moderate and severe subgroups. The measurement method is described in the text according to figures on the right.

Termination

The terminal phase was easy to determine in normal subjects. The starting point of deceleration from the handle velocity which had been maintained at the target velocity was different in each trial and from case to case. Some of the subjects began to decelerate the handle velocity before the target stopped, while others began deceleration after recognition of target arrest. For the normal subjects, in the trials at 7.5 deg/s target velocity, the starting points of deceleration were mostly distributed between 400 ms before and 300 ms after target arrest (fig. 10, N).

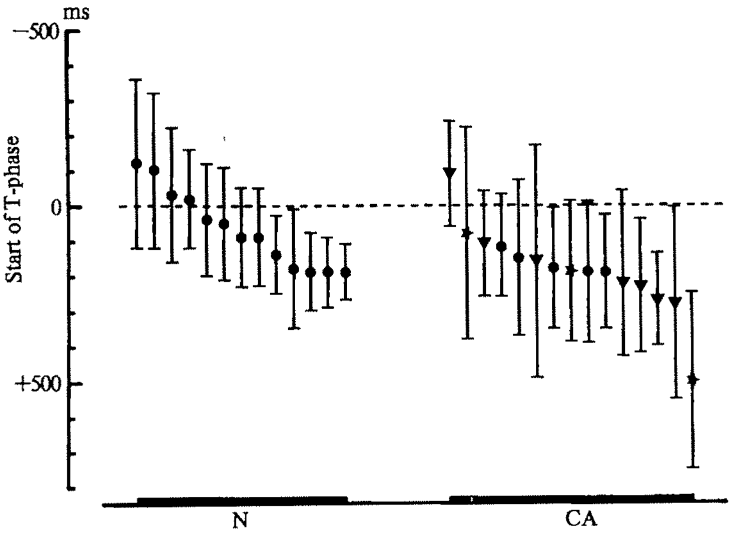

FIG 10. Distribution of end of the pursuit phase. N = normal group; CA = cerebellar ataxia patients

In the cerebellar ataxia patients, especially when the saccadic pattern in the M-phase was prominent, the point of deceleration was sometimes difficult to determine on the $\dot{D}$ traces. In such cases, the last peak of undulation in the M-phase on $\dot{D}$ traces was regarded as the starting point of deceleration. Thus measured, the starting points of deceleration in the cerebellar ataxia patients were distributed between 300 ms before and 800 ms after target arrest (fig. 10, CA). Compared with the control group, the patients tended to be much slower to begin deceleration. There was no relationship between the clinical severity and amount of delay in the onset of deceleration. Another notable feature of the cerebellar ataxia patients in the T-phase was difficulty in reaching the final target point quickly. It took them several trials before they were able to reach final position after target arrest.

EMG Analysis

For all normal subjects, the EMG pattern was fairly uniform (fig. 2). In the slowest tracking movement, there was a brief burst of action potentials at the beginning of the handle movement in the agonist biceps muscle. This was directly followed by a short silent period, which gave way to the tonic discharge which continued throughout the M-phase. After the subject stopped moving, EMG activity gradually decreased but was maintained to some extent throughout this period during which the handle was held in the flexion position. The antagonist muscle (triceps) was generally silent. When the target velocity increased, the biceps EMG pattern did not change qualitatively but the triceps muscle tended to show a brief EMG discharge in the I-phase corresponding to the short silent period of the biceps EMG activity. In general, the reciprocal EMG pattern for the normal subjects was well maintained throughout the tracking task.

In the cerebellar ataxia patients, the EMG patterns were quite different. Cocontraction of the antagonistic muscles was observed in about half the cases (fig. 3). The I-phase did not demonstrate the triphasic pattern which was typical for the control subjects (brief EMG burst followed by a short silent period followed up by a continuous tonic discharge in the agonist, and a reciprocal brief discharge in the antagonist at a higher speed), but instead consisted of irregular EMG activity which was directly connected to the tonic discharge of the M-phase. In some cases, as shown in fig. 3, EMG activity was observed before the start of tracking. In the M-phase, instead of a smooth and gradual increase of tonic discharge as found in the control group, the amount of EMG discharge showed a marked fluctuation, reflecting saccadic tracking movements.

DISCUSSION

Reaction Time

Our findings were consistent with previous studies which also demonstrated that the reaction time increases in cases of cerebellar dysfunction (Holmes, 1917, 1922, 1939; Rondot *et al.*, 1979). However, it should be noted that reaction time for controls in our study was somewhat longer than those of other studies, particularly during the slower target velocity sessions (fig. 4). Previous investigators presented reaction time values of 240 to 260 ms for elbow flexion movement in normal subjects (Searle and Taylor, 1948; Flowers, 1975, 1976) while, in our study, reaction time values ranged from 210 to 390 ms. The differences in experimental conditions may account for the discrepancy. The previous studies were made on ballistic or step movements in which the primary concern was quickness of movement initiation rather than accuracy. In our study, not only quickness but also accuracy was required. A smooth transition to the pursuit phase was also a necessary factor in our task. Possibly a more important factor for consideration was that the reaction time was most delayed in the session with the slowest target velocity, and became shorter as the target velocity increased, reaching the value comparable to that of the step experiment at 30 deg/s in many control subjects. The initial error size at the slowest target session was around 2 or 3 deg, which is notably small when compared with an average 10 deg during the fastest target session (fig. 5). However, this factor alone could not explain the shortening of reaction time since the reaction time did not change significantly in the step tracking experiment as the test step size decreased (Craik and Vince, 1943; Flowers, 1976; Poulton, 1974; Searle and Taylor, 1948). At present, we think that target velocity may influence perception of target movement: the slower the target velocity, the more difficult it is for the subject to recognize the onset of target movement.

What are the mechanisms causing the delay in reaction time in cerebellar ataxia? The possibilities to be considered are (1) failure to begin the task effectively due to the cocontraction between the agonist and antagonist muscles; (2) delay in the quick and effective recruitment of spinal motoneurons, which may have been less excitable as a result of the cerebellar hypotonia; and (3) the delay in consolidation of motor commands and/or in the transmission of commands from the higher motor centres to the spinal motoneurons.

The first explanation seems improbable, as the cerebellar ataxia subjects without a cocontraction pattern (about half of the test samples) showed no better results in reaction time than those with cocontraction patterns. In addition to this, the major portion of delay in reaction time consisted of a longer premotor time.

The second possible explanation implies that the descending motor command may require a longer time both to bring up agonist motoneurons with low excitability to the firing level, and also to recruit a certain number of those motoneurons for effective transmission of muscle contraction to the load (forearm and handle). However, the exact time intervals from the arrival of the descending command to the motor pools, to their activation and then to the appearance of the EMG, which composes a part of the premotor time, cannot be estimated. When considering the effective handle movement, the motor time of patients with cerebellar ataxia, except for the severe cases, did not differ significantly from that of the control group. This possibility may have contributed in a minor way to the delay of reaction time, but the extent of its influence could not be determined in the present study.

The finding that the major delay occurred in the premotor time would support the third possibility most strongly. There are data available from animal experiments which also support this possibility. Meyer-Lohman *et al.* (1977) demonstrated, using cebus monkeys trained to make a prompt elbow movement in response to a visual signal, that localized cooling of the dentate nucleus caused a significant delay in reaction time. This delay accompanied a comparable delay in the onset of unitary discharges of movement-related neurons in the motor cortex. Similar results were also obtained in an experiment carried out on monkeys with chronic lesions of cerebellar nuclei by Lamarre and Jacks (1978). These results indicated the participation of the cerebellum in generating motor commands for prompt volitional movements.

Initial Peak Velocity

The initial peak velocity (IPV) augmented its size in accordance with the increase in target velocity in the normal subjects. This phenomenon provides an adequate index for the evaluation of motor skill in the I-phase. Nagaoka and Tanaka (1980) suggested that the IPV in the ramp tracking was a centrally programmed response, as is the case in step tracking (*see* Introduction). The major reasons for this assumption were the brief duration of the IPVs, corresponding burst EMG activity in the agonist muscles, and its relatively stereotyped pattern. The finding that patients with tabes dorsalis have normal regression lines of IPV (Beppu *et al.*, 1981) indicates independence of the catch-up reaction from somatic sensory information. A loss of ability by the cerebellar ataxia patients to produce an appropriate IPV in the present study supports the above idea. Yet it must be noted that there was a subtle difference in the catch-up reactions between the usual step and ramp tracking. This difference will be referred to below in the *EMG pattern* section.

Deterioration of the linearity in the initial error-IPV relationship in the cerebellar ataxia group was regarded as a defect in consolidation of motor programs for accurate IPV output. This problem will also be discussed from a different point of view in the next section. Not only a widely variable reaction time, but also difficulty in selecting an appropriate and stable size of IPV for a given initial error, could have caused this deterioration. The degree of deterioration roughly corresponded to the clinical severity of the patients. Although it varied between cases, in some this feature was clearly demonstrated during the course of recovery from cerebellar ataxia. Patients suffering from Wallenberg's syndrome resulting from brainstem infarction showed a gradual and steady recovery of the initial error-IPV relationship which corresponded with the recovery of clinical signs (*see* fig. 4 in Beppu *et al.*, 1983).

Saccadic Pattern in the Middle Pursuit Phase

A typical pursuit pattern during the M-phase in normal subjects involved the handle movement matching a fairly constant velocity, which conformed to the rate tracking pattern (*see* Poulton, 1974). In contrast to the execution of movement in I-phase, which depended mostly upon the central program mechanism, the M-phase provided ample opportunity for the contribution of an error-correcting mechanism using both visual and proprioceptive feedback information or a closed-loop system. In principle, both senses should be able to carry information concerning not only limb position but also velocity. Nagaoka and Tanaka (1981) had shown that visual information for arm movement alone was not enough to assure a smoothness in slow visuomotor tracking movement. Proprioception or kinaesthesia is essential for smooth tracking. This was noticed in the subjects with sensory ataxia who failed to maintain a normal pursuit pattern showing marked undulations in $\dot{D}$ traces while maintaining a normal initial catch-up reaction (Beppu *et al.*, 1981). However, even with both visual and proprioceptive information secured, a simple negative feedback system may fail to prevent a saccadic response pattern, which is present in the position tracking pattern (*see* Poulton, 1974). Miles and Evarts (1979) stressed the importance of the positive feedback loop, which sends back the 'efference copy,' enabling a smooth pursuit. Taken together, the normal subjects may follow the target smoothly by integration of all these motor control systems: a rough estimation with the open-loop system and a fine corrective adjustment with the closed-loop system, as stated by Searle and Taylor (1948).

The saccadic pattern with catch-up and arrest responses in cerebellar ataxia patients differed qualitatively from the pattern in patients with sensory ataxia. In the latter, the saccade frequency of handle movement seldom showed a true arrest phase, and the frequency of undulations in handle velocity was generally higher than that of the cerebellar ataxia patients (Nagaoka and Tanaka, 1981). These findings imply that the pathological motor mechanism of cerebellar ataxia does not lie in a simple defect in transmission of proprioceptive feedback information as is the case with sensory ataxia; nor is it caused by a primary defect in the motor system which may generate slow continuous movements (fig. 8). Instead it is both a defect in computing the afferent information for its comparison with the expected motor output, and also of adapting the computed results for timely and accurate correction of the forthcoming motor programs. Taken together, the most plausible hypothesis for the saccadic tracking pattern in cerebellar ataxia patients is that, in contrast to the normal subject who is able to make a smooth transition from an initial catch-up reaction to constant velocity pursuit, the patient is unable to carry out such a transition. This would be because of dysmetria at the initial response and of failure to link the programs for the catch-up reaction and constant pursuit. The patient is therefore obliged to stop and to repeat the catch-up reaction, guided by visual information. The saccadic pattern represents repeated *voluntary corrective responses* (*see also* Concluding Remarks).

In keeping with this, it can also be said that patients are able to perform step movements, although not adequately, if they are requested to match a response with target movement. In this context, there are several pieces of evidence indicating that the cerebellum is essential for visually controlled movements. This does not necessarily imply biased importance for fast movements alone (Stein, 1978; Mano and Yamamoto, 1980). The present findings are in agreement with previous studies, particularly of Mano and Yamamoto (1980) who presented simple spike discharge patterns of Purkinje cells from the cerebellar hemisphere of monkeys during visually guided wrist flexion-extension tracking movements. These patterns conformed well to the velocity trajectory of movement, which suggested that the Purkinje cell dealt with velocity as the major component of movement. This could be related to the present results which showed failure on the part of the cerebellar ataxia subjects to control the movement velocity for smooth pursuit as well as initial catch-up.

Terminal Phase

The action taken by the control subjects during the beginning of the T-phase varied from case to case. In some, handle movement tended to decelerate before target arrest, in others just as the target became arrested, and in still others, after the target had stopped. In the majority of cases, performance in the T-phase may have depended upon anticipatory reactions. Since the terminal position of the target on the display was unchanged and the approach velocity was constant in each session, the subject could easily have foreseen the timing of target arrest. Thus, whether the subject decelerated the handle before, during or after target arrest seemed to depend more upon his attitude rather than his motor skill. When analysing the performance in the terminal stage, it will therefore be necessary to prepare other experiments based upon a different paradigm. In general; the patients with cerebellar ataxia tended to begin deceleration later than the normal controls. This phenomenon may support the statement by Holmes (1939), '*slow to stop*'.

EMG Pattern

In the initial catch-up reaction of ramp target with the fastest velocity, EMG activity in normal subjects tended to show the typical triphasic pattern: bursts of activity first in the agonist muscle, then in the antagonist muscle with a brief silent period in the agonist, and finishing the pattern with activity again in the agonist muscle. This finding was in principle the same as the previous findings in ballistic or step-mode movements (Wachholder and Altenburger, 1926; Terzuolo and Viviani, 1973; Hallett *et al.*, 1975*a*; *see also* Basmajian, 1978). This pattern was regarded as centrally programmed (Hallett *et al.*, 1975*a*; Brooks and Thach, 1981). In contrast, in the sessions where slower target movement was used, antagonistic burst activity disappeared while the EMG pattern in biceps remained essentially the same. Recently, such an EMG pattern has been shown in fast movements of the human thumb and elbow by Marsden *et al.* (1983). According to these authors, the antagonist burst decreased or disappeared during three conditions of movement: slower movements, movements of long distance and movements which were halted mechanically. The present study, however, cannot be compared directly with the study by Marsden *et al.* (1983), since the latter was principally a step task with movement velocities of several hundred deg/s whereas the former was a ramp task in which IPV sizes were mostly less than 100 deg/s and the initial response had to be transferred smoothly to the pursuit movement. At any rate, we agree with their conclusion that the size and timing of the bursts of muscle activity are subtly adjusted to the precise nature of the task. Fruitful discussion on this matter will be possible after a quantitative study similar to that of Marsden *et al.* (1983) for the present ramp task.

In the cerebellar ataxia patients the EMG pattern was quite variable, reflecting the ever-fluctuating tracking movements in each trial. In general, the triphasic EMG pattern in the I-phase was distorted (*see* Hallet *et al.*, 1975*b*). There was often continuous background discharge during the waiting period even after the movement was well practised. The initial burst of biceps activity showed a gradual increase which directly passed into the tonic discharges of the M-phase. In about 50 per cent of the patients, a significant amount of EMG activity was observed simultaneously in the agonist and antagonist muscles. Such cocontractions were never observed in the normal subjects. There was no clear correlation between the antagonistic cocontraction and the clinical severity or type of cerebellar ataxia, for example, the presence of extrapyramidal features in some cases of cerebellar degeneration. Cocontraction of the antagonistic muscles in voluntary movement has been reported both in patients with cerebellar deficits (Terzuolo and Viviani, 1973; Rondot *et al.*, 1979) and cerebellectomized monkeys (Lammare and Jacks, 1978; Soechting *et al.*, 1976). The reason why the antagonistic cocontraction occurred in some of the patients with cerebellar ataxia and not in others has yet to be investigated. It could be from an essential defect in the motor programming mechanism or a direct result of compensatory reaction by the subject's endeavour to minimize the error due to cerebellar deficits, such as dysmetria and hypotonia. At any rate, it is certain that the tracking pattern in cerebellar ataxia is to some extent modified by the antagonistic cocontraction.

Concluding Remarks

In the present study our aim was to evaluate motor ability of patients with cerebellar ataxia in a slow visuomotor tracking task. The present ramp tracking task was eventually found to be useful for the analysis both of movement initiation and execution during slow movements. Several characteristic features in various phases of the tracking performance were revealed as discussed above. Their correlation with the clinical signs in simple movements as defined by Holmes (1939; *see also* 1917, 1922) is discussed below.

The clinical sign of *slow to start and slow to stop* is well demonstrated in the findings in reaction time of the initial and terminal phases, and also in the pursuit phase of repeated catch-up and arrest patterns. Massion and Sasaki (1979) have discussed the importance of delicate cerebrocerebellar relations for timely initiation of movement and we choose to add no more to their discussion. Nevertheless, one question still remains unanswered: to what extent does hypotonia influence movement initiation? Gilman (1969) demonstrated a marked depression of the fusimotor system after cerebellar lesions in the monkey, which is akin to humans. However, hypofunction of the fusimotor system may not play a major role in the delay of movement initiation since Vallbo (1971) showed that the facilitatory command *via* the fusimotor system reaches alpha motoneurons only after movement is initiated.

The present study could not deal with the quantitative aspect of dysmetria because of limitations of space, although the sign was evident in the original records—the deterioration of initial error-IPV relationship and MAP ratio. This problem will be considered in a separate paper. It should be pointed out here that hypometric tracking was more pronounced than hypermetric. This may be related to the present task in which target movement was relatively slow and accuracy as well as rapidity of reaction was requested of the subject. The mechanism of dysmetria may be attributed not only to an inadequate consolidation of motor programs in timing and size but also to a defect in the comparator function.

The question of cerebellar tremor in voluntary movement is rather ambiguous since *tremor* is an involuntary movement. Clinicians have considered that some aspects of cerebellar tremor result from conscious effort to correct preceding dysmetric reactions (Holmes 1939; Dow and Moruzzi, 1958; DeJong, 1979). The saccadic pursuit pattern in the present study is voluntary (*see above*) and thus should be differentiated from action tremor, such as the one visible in patients with lesions of the dentatorubral system. We have tested a few such cases and have observed quite a different pursuit pattern (fig. 11). A forward and backward oscillatory movement appeared, superimposed on the net pursuit movement and continuing long after target arrest. Velocity traces showed reverse deflections in

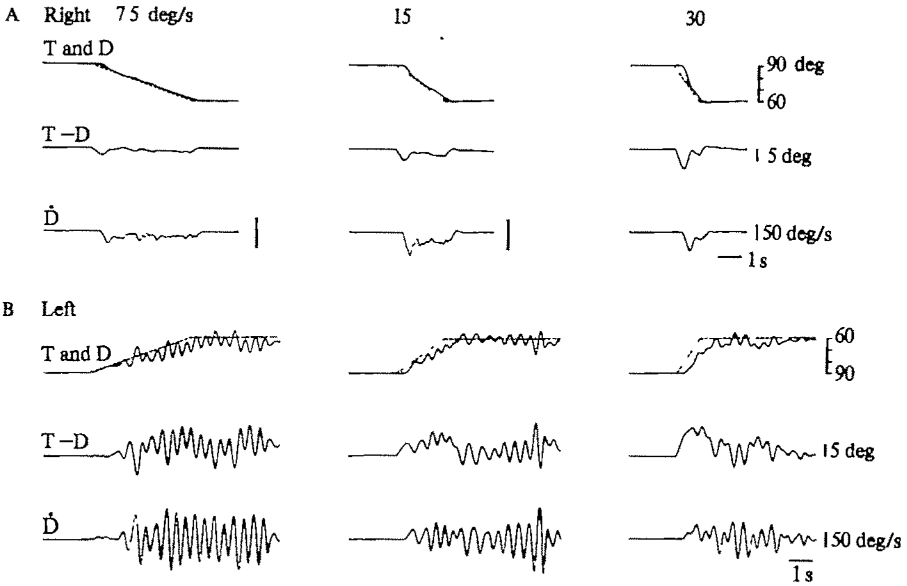

FIG 11. Tracking pattern of a patient with intention tremor due to a cerebrovascular lesion of the dentatorubral system A, unaffected right side, B, affected left side.

accordance with backward movement. This pattern would be categorized as *terminal tremor* (Holmes, 1939; DeJong, 1979). Its frequency was highly regular, scarcely varying during each trial or target velocity change. These features thus indicate an involuntary tremor. The most conspicuous characteristic, which discriminates the two types of undulations in ramp-tracking movements, is that the patients in the present study showed clear movement arrest while patients with terminal tremor did not. This irregularity and clear arrest in movement would aid in differentiation. It may be difficult to decide in the clinic to what extent movements in patients are involuntary, but a careful examination of these characteristics would be helpful.

We know that many other problems concerning the pathological motor mechanisms underlying cerebellar ataxia still remain unsolved, but we expect that further studies arising out of the present investigation will provide us with much invaluable information.

ACKNOWLEDGEMENTS

The authors wish to express their thanks to Professor T. Tsubaki for his encouragement throughout this study, and Professor N. Yanagisawa for critically reading the manuscript. The assistance of Mr K. Shinozaki in electronics and computer programming, of Ms K. Nomura during the study and in the preparation of the manuscript, and of Ms Joan Ryan for scrutinizing the English, is also gratefully acknowledged. This work was partly supported by a Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture (No. 311410) and by a grant from the Research Committee on Ataxia from the Ministry of Health and Welfare, Japan.

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(*Received August 25, 1983. Revised December 28, 1983*)

Brain (1984), **107**, 811-827

LEXICAL AGRAPHIA

FURTHER SUPPORT FOR THE TWO-SYSTEM HYPOTHESIS OF LINGUISTIC AGRAPHIA

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SUMMARY

Eight patients with acquired agraphia were studied using the same writing tests and were compared with normal and brain-damaged controls. Four patients fulfilled the criteria for lexical agraphia and on CT scan had lesions of the posterior angular gyrus that spared the supramarginal gyrus. The other 4 fulfilled the criteria for phonological agraphia. They had lesions on CT scan that were similar to those found in previously described patients with phonological agraphia. Their lesions involved the supramarginal gyrus or insula deep to it and spared the angular gyrus. These studies support the hypothesis that there are two dissociable spelling systems and that these spelling systems are disrupted by focal lesions in separate but distinct brain regions.

Further studies investigated the relationships between phonological agraphia and phonological dyslexia (alexia), and lexical agraphia and surface dyslexia (lexical alexia). The data support the hypothesis that individual systems subserve the four processes of phonological spelling, phonological reading, lexical spelling and lexical reading.

INTRODUCTION

Since Ogle (1867) first defined agraphia, most analyses of agraphic patients have primarily been descriptive, and the agraphias have been delineated mainly by their associations with other neuropsychological disorders (Head, 1926; Nielson, 1946; Leischner, 1969; Hécaen and Albert, 1978; Benson, 1979; Kaplan and Goodglass, 1981). Consequently types of agraphia have included aphasic agraphia (agraphia with Broca's, Wernicke's or conduction aphasia), agraphia with alexia, constructional agraphia (agraphia associated with visual-spatial disability), apraxic agraphia (agraphia associated with limb apraxia) and pure agraphia (agraphia in the absence of other neuropsychological disorders).

There are two general difficulties with these traditional subdivisions of the agraphias. First, there is substantial variability within a given type of agraphia. Patients with a specific aphasic agraphia may have agraphias that differ considerably. For example, some patients with Broca's aphasia have agraphias that more closely resemble the agraphias of patients with Wernicke's aphasia than the agraphias of other patients with Broca's aphasia (Roeltgen *et al.*, 1983). Secondly, there is difficulty in delineating the cerebral anatomy underlying a type of agraphia. For example, pure agraphia has been described in patients with lesions in multiple cerebral sites, including the second frontal convolution (Exner's area) (Aimard *et al.*, 1975; Hécaen and Albert, 1978; Marcie and Hécaen, 1979; Kaplan and Goodglass, 1981), the superior parietal lobule (Basso *et al.*, 1978), the posterior perisylvian region (Auerbach and Alexander, 1981; Rosati and De Bastiani, 1979) and the region of the left caudate and internal capsule (Laine and Marttila, 1981).

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In contrast to classification based on descriptive analysis, some authors have attempted to analyse the functions necessary for writing. Goldstein (1948) delineated two groups of such functions. He described writing mechanisms associated with language and writing mechanisms associated with the motor output necessary for writing. Although disorders of any of these mechanisms produce agraphia, the agraphias in one group differ substantially from those in the other. Disorders involving the former mechanisms are frequently associated with aphasia. The errors produced usually are spelling errors. In these disorders written letters, graphemes, are usually well formed. In contrast errors due to disruption of the motor mechanisms of written spelling frequently consist of poorly formed graphemes. Because of these differences among agraphic types, it is important to distinguish between the agraphias due to disruption of the writing mechanisms associated with language and those due to disruption of mechanisms associated with motor output. We have previously suggested that the former group of agraphias be termed the linguistic agraphias and the latter group the motor agraphias (Roeltgen, 1983).

Recently some investigators have attempted to refine further the linguistic agraphias (Beauvois and Dérouesné, 1981; Shallice, 1981; Bub and Kertesz, 1982; Roeltgen, *et al.*, 1982*a*; Campbell, 1983; Roeltgen *et al.*, 1983; Hatfield and Patterson, 1983). Such analyses have suggested that there are at least two types of linguistic agraphia, phonological agraphia (Shallice, 1981; Roeltgen *et al.*, 1983) and lexical agraphia (Beauvois and Dérouesné, 1981).

Patients with phonological agraphia are said to have difficulty spelling pronounceable nonwords (e.g. flig) with some preserved ability to spell orthographically irregular words (words that cannot be spelled by direct speechsound to letter (phoneme to grapheme) conversion (e.g. knife)). These patients usually make errors that are not phonologically correct (e.g. concer for corner) (Shallice, 1981; Roeltgen *et al.*, 1982*a*, 1983). In this study the term spelling is used to indicate oral spelling and/or writing. Although both functions should be affected equally in the linguistic agraphias, this is not always the case. Some patients may have limb paralysis or apraxic agraphia and cannot write, while others may have expressive speech deficits and cannot spell. Therefore not all patients with linguistic agraphias have been studied using the same output mode.

In contrast, one patient has been described with what has been termed lexical agraphia (Beauvois and Dérouesné, 1981). That patient spelled nonwords correctly but had difficulty spelling irregular and ambiguous words (words containing speech sounds that can be spelled by more than one letter, e.g. breeze). His errors were usually phonologically accurate (e.g. gelosy for jealousy). A similar patient has been described by Hatfield and Patterson (1983), although their patient was not tested with nonwords.

These studies have led to the contention that there are two distinct spelling systems, one phonological and one lexical or orthographic. The former is thought to be necessary for spelling orthographically regular words (e.g. animal) and nonwords, and the latter for irregular words.

There are, however, certain questions raised by these studies. First, it is not definitely known that lexical agraphia is a reproducible syndrome, in that only one patient has been described who fulfils all the criteria for this disorder. A second problem involves a possible overlap between the syndromes of phonological and lexical agraphia. This arises because patients with phonological and lexical agraphia have not been examined using the same tests, especially the same irregular words. Although patients with phonological agraphia spell some irregular words correctly, it is not certain that their ability to spell irregular words is any better than that of the patients with lexical agraphia. Perhaps phonological agraphics have a difficulty in spelling nonwords superimposed on a difficulty in spelling irregular words but remain able to spell some irregular words. A third problem involves possible anatomical loci for these disorders. Although it has been postulated that the supramarginal gyrus (Roeltgen *et al.*, 1983) or underlying insula (Roeltgen *et al.*, 1982*a*) is an important anatomical substrate for phonological agraphia, little is known about a possible anatomical substrate for lexical agraphia. Finally, there is uncertainty as to whether phonological and lexical agraphia are distinct disorders or whether they reflect more generalized disorders within the phonological and lexical systems.

We have attempted to address these issues by studying 4 patients with acquired agraphia who fulfilled the criteria for lexical agraphia. We compared the ability of these patients to spell with that of 4 new patients who fulfilled the criteria for phonological agraphia. We also compared these groups with two groups of control subjects (normal and with focal brain lesions). Next, using the results of computerized tomography (CT) we attempted to define a possible anatomical locus for lexical agraphia and to compare this locus with that suggested for phonological agraphia. We also analysed the reading ability of these patients in an attempt to determine the relationships between phonological and lexical agraphia and phonological and surface (lexical) dyslexia.

CASE REPORTS

Lexical Agraphia

Case 1. This 69-year-old, high school educated, right-handed male presented to the hospital with the complaint that he could not read. Before his illness he had been good at spelling and reading. Studies of control subjects have shown that individuals who describe themselves as good or excellent (in contrast to fair or poor) and have an educational level of more than the eighth grade usually do well on our reading and writing tests (Roeltgen *et al.*, 1984). Case 1 was assessed two weeks after the onset of his symptoms. On the Western Aphasia Battery (WAB) (Kertesz, 1980) his scores were consistent with a mild anomic aphasia (Table 1). He also had an alexia and agraphia (*see* Special Tests). When spelling was tested, he spelled nonwords well but had more difficulty spelling irregular words than regular words (Table 2). His spelling errors were frequently phonologically correct (e.g. wepon for weapon). A CT scan showed a left parieto-occipital haemorrhage.

Case 2. This 61-year-old, college educated, right-handed female initially noted difficulty in 'finding words'. Before her present illness she had been good at spelling and reading. She was assessed two weeks after the onset of her symptoms. On the Western Aphasia Batter (WAB) (Kertesz, 1980) her scores were consistent with the diagnosis of a mild anomic aphasia (Table 1). She also had an alexia and agraphia (*see* Special Tests). When spelling was tested she spelled nonwords well but had more difficulty spelling irregular than regular words (Table 2). Many of her errors were phonologically correct (e.g. misell for missile). A CT scan showed a left parieto-occipital enhancing lesion as well as small left frontal and right occipital enhancing lesions. The clinical diagnosis was metastatic lung carcinoma.

Case 3. This 32-year-old, high school educated, right-handed female developed blurred vision in her right visual field three weeks before being admitted to hospital. Before her illness she had been good at spelling and reading. A CT scan showed a left parieto-occipital lesion. A left occipital craniotomy and biopsy showed evidence of demyelinating disease. She was assessed two weeks after operation. On the WAB her scores were consistent with the diagnosis of a very mild anomic aphasia (Table 1). She also had a mild alexia and an agraphia. When spelling was tested she spelled nonwords perfectly but had more difficulty spelling irregular words than regular words (Table 2). Many of her errors were phonologically correct (e.g. mischef for mischief). A repeat CT scan performed postoperatively revealed a lesion of the left medial occipital lobe and the lateral superior parietal lobule. In addition it undercut the lateral occipital gyrus and part of the posterior middle temporal gyrus.

Case 4. This 86-year-old, high school educated, right-handed female had an ischaemic cerebral infarction while in hospital for coronary artery disease. Before her illness she had been excellent at spelling and reading. She was evaluated two weeks following her stroke. Clinically she had a mild

TABLE 1 RESULTS FOR THE WESTERN APHASIA BATTERY*

Case No.	*Information content***	*Fluency*	*Comprehension*	*Repetition*	*Naming*
1	10	10	8.2	9.3	7.1
2	9	9	8.1	9.4	6.4
3	9	9	8.9	9.8	9.0
4	8	6	7.8	6.1	6.8
5	10	9	9.9	9.8	9.1
6	9	5	9.0	9.0	8.3
7	9	9	8.0	8.0	9.4
8	10	8	9.7	9.5	9.1

* Kertesz (1980). ** Maximum possible score = 10.

Wernicke's aphasia but her scores on the WAB were consistent with the diagnosis of a mild conduction aphasia (Table 1). She also had a mild alexia and an agraphia. When spelling was tested she spelled nonwords relatively well, but had more difficulty spelling irregular than regular words (Table 2). Most of her errors were phonologically correct (e.g. soverin for sovereign). A CT scan showed an enhancing cortical lesion that involved a portion of the posterior temporal lobe, the angular gyrus, the parieto-occipital lobule and the lateral occipital gyrus on the left.

Phonological Agraphia

Case 5. This 82-year-old, high school educated, right-handed male developed 'trouble finding words' a few months before he was evaluated. At that time he was diagnosed as having had an ischaemic cerebral infarct. Before his stroke he had been good at spelling and reading. On the WAB he obtained scores consistent with a very mild anomia (Table 1). He had a very mild alexia (limited to nonwords) and an agraphia. When spelling was tested he had difficulty spelling nonwords but no more difficulty spelling irregular than regular words (Table 2). His errors were usually not phonologically correct (e.g. barvage for beverage). A CT scan revealed a lesion of the left frontoparietal region and the insula deep to the anterior supramarginal gyrus.

Case 6. This 71-year-old, high school educated, right-handed male had an ischaemic cerebral infarct a few years prior to being evaluated. Before his stroke he was good at spelling and reading. On the WAB he obtained scores consistent with a mild anomic aphasia (Table 1). He also had an alexia and an agraphia. When spelling was tested, he was unable to spell nonwords but had no more difficulty spelling irregular than regular words (Table 2). His errors were usually not phonologically correct (e.g. glim for limb). A CT scan showed a lesion involving the left anterior and middle perisylvian region, including the frontal operculum and insula.

Case 7. This 26-year-old, college educated, right-handed male had an ischaemic cerebral infarct two years prior to being evaluated. Before his stroke he was good at spelling and reading. Clinically he had a mild Wernicke's aphasia but on the WAB he obtained scores consistent with the diagnosis of an anomic aphasia (Table 1). He also had a mild to moderate alexia and an agraphia. When spelling was tested he had considerable difficulty spelling nonwords but had no more difficulty spelling irregular words than regular words (Table 2). His errors were usually not phonologically correct (e.g. graicer for glacier). A CT scan showed a lesion involving the left anterior inferior supramarginal gyrus, the junction of the superior temporal gyrus and angular gyrus, the posterior middle temporal gyrus and the lateral occipital gyrus.

TABLE 2 SPELLING ABILITY OF INDIVIDUAL PATIENTS

Case No	*Non-words*	*Regular words**	*Irregular words**	*Difference between regular and irregular*	*Ambiguous**			*Nouns***	*Function words***
					Low	*Medium*	*High*		
1	90	67	28	39	100	90	30	100	80
2	90	72	53	19	100	88	70	85	100
3	100	86	58	28	100	100	90	100	100
4†	70	67	39	28	80	80	70	90	90
5	48	71	68	3	85	95	90	98	89
6	0	30	25	5	60	50	30	65	40
7	10	44	40	4	90	70	70	95	55
8	30	56	69	−13	80	90	90	100	85

Results expressed as percentage correct * Regular and irregular words and the 3 groups of ambiguous words were matched for length, frequency (Thorndike and Lorge, 1944), imageability (Paivio *et al*, 1968) and word class. ** Nouns and function words were matched for length, frequency and regularity. † In all tests the patient wrote and spelled aloud. Minor variations occurred between modalities but there were no systematic differences The results listed are combined scores.

Case 8. This 54-year-old, high school educated, right-handed female had an ischaemic cerebral infarct one month prior to being evaluated. Before her stroke she was good at reading and spelling. On clinical examination and on the WAB she had a very mild aphasia that could not be adequately classified (Table 1). She also had a mild alexia and an agraphia. When spelling was tested, she had difficulty spelling nonwords but had no more difficulty spelling irregular words than regular words (Table 2). Her errors were usually not phonologically correct (e.g. corcer for corner). A CT scan showed a lesion of the left middle perisylvian region that involved almost exclusively the insula and subcortical white matter. The only definite opercular involvement was at the anterior aspect of the supramarginal gyrus.

SPECIAL TESTS

At different times, each patient was asked both to spell orally and to write some of the same words. When asked to spell or write, all patients were requested to repeat the words and nonwords. All patients except for Case 6 performed this task without difficulty. This patient repeated words well but had some difficulty repeating nonwords. Three patients had apraxic agraphia (Cases 1, 3 and 4) and spelled aloud better than they wrote. Therefore, their spelling ability was tested by having them spell orally. Two patients (Cases 7 and 8) performed better with writing than with oral spelling. Both these patients showed similar error patterns when spelling and writing. However, they made more errors when spelling aloud than when writing. (On the same word lists, Case 7 was correct on 75 per cent of words when writing and 35 per cent when spelling. Case 8 was correct on 93 per cent of words when writing and 78 per cent when spelling.) Because the error patterns were similar, it was felt the differences in performance were due to dysfunction in the motor output of oral spelling. Complete testing was therefore accomplished by having the patients write. The remaining patients appeared to have similar ability to write and spell aloud as reflected by an equal number of errors and similar error patterns when writing or spelling aloud. (On the same word lists, Case 2 was correct on 74 per cent of words when writing and 75 per cent when spelling. Case 6 was correct on 80 per cent of words when writing and 84 per cent when spelling. Case 5 refused to write more than a few words.)

In addition to the two patient groups, two groups of control subjects were given the tests. One group consisted of 4 age-matched subjects with focal brain lesions involving the left frontal and right parietal lobe, the other consisted of 4 age-matched subjects without brain injury. All control subjects were educated to greater than the eighth grade and described themselves as being good or excellent at spelling and reading. As well as attempting to spell each of the words, the two groups of patients and the normal control subjects also attempted to read each word and nonword.

Spelling Nonwords

In order to test the phonological spelling system, we tested the ability of each patient to spell 20 one- and two-syllable nonwords (Table 2). The 4 patients classified as having lexical agraphia correctly spelled 88 per cent (Table 3). In contrast the phonological agraphic group correctly spelled only 22 per cent of nonwords.

The results obtained from the two control groups were similar to those obtained from the lexical agraphic group. The control groups correctly spelled 90 per cent (brain-damaged groups) and 98 per cent (nonbrain-damaged group) (Table 3).

TABLE 3 MEAN SCORES ON SPELLING TESTS FOR LEXICAL AGRAPHICS, PHONOLOGICAL AGRAPHICS, CONTROL SUBJECTS WITH FOCAL BRAIN LESIONS AND NORMAL CONTROLS

Patient group	*Non-words*	*Regular*	*Irregular*	*Difference between reg and irreg*	*Ambiguous*			*Nouns*	*Function words*
					Low	*Medium*	*High*		
Lexical agraphic	88	73	44	29	95	88	65	94	93
Phonological agraphic	22	50	50	0	79	76	70	90	68
Brain-damaged controls	90	93	86	7	100	100	98	100*	100*
Normal controls	98	96	92	4	100	100	98	100	100

Results expressed as percentage correct * Based on 3 subjects (one was not tested with nouns and function words)

Spelling Regular and Irregular Words

In order to test the lexical spelling system, we tested the ability of each patient to spell matched regular and irregular words and calculated the difference between the number of correctly spelled regular and irregular words (Table 3). Words were considered regular if they could be spelled and read by an algorhythmic (letter by letter) sound-to-letter or letter-to-sound conversion (e.g. moment, letter, nutmeg). With the exception of words with double vowels (e.g. speech, green), words were considered irregular if they could not be spelled and read by an algorhythmic (letter by letter) method (e.g. jealousy, marriage, glacier). Words were included only if they were irregular for both spelling and reading. (The words used are listed in the Appendix.) The words were matched for length, frequency of occurrence (Thorndike and Lorge, 1944), 'imageability' (Paivio *et al.*, 1968) and word class (all were nouns). Some patients and controls were tested with 36 regular and irregular words and others were tested with 45 of each type. This difference occurred because we expanded our word lists during the study. The 4 patients classified as having lexical agraphia correctly spelled 73 per cent of irregular words and 44 per cent of regular words for a difference of 29 per cent. In contrast, the phonological agraphic group correctly spelled 50 per cent of regular and irregular words, showing no difference between the two. Similarly, the control groups correctly spelled 93 per cent regular and 86 per cent irregular for a difference of 7 per cent (brain damaged), and 96 per cent regular and 92 per cent irregular for a difference of 4 per cent (normal).

Spelling Ambiguous Words

In order to examine the lexical system further, we tested the ability of each patient to spell words of varying ambiguity. A word was considered to have a low degree of ambiguity if there was only one acceptable spelling that could produce the correct phonology (e.g. charm). A word was considered to have medium ambiguity if one phonetic sequence could be represented by more than one letter combination (e.g. brain may be spelled brain or brane with the same resulting phonology). A word was considered to have high ambiguity if it had two or more phonetic sequences that could be represented by more than one letter combination (e.g. cotton may be spelled cotton, kotton or cotten with the same resulting phonology). All three groups were matched for length, frequency of occurrence (Thorndike and Lorge, 1944), imageability (Paivio *et al.*, 1968) and word class (all were nouns). (The ambiguous words are listed in the Appendix.) Each patient was given 30 words, 10 in each group. The 4 patients classified as having lexical agraphia showed a large difference between ability to spell words of high ambiguity and words of low ambiguity. They spelled correctly 95, 88 and 65 per cent words of low, medium and high ambiguity respectively. The phonological agraphic group and control groups did not show this difference (Table 3).

Spelling Nouns and Function Words

In order to evaluate the effect of word class on the spelling ability of our patients, we asked them to spell 20 nouns and function words. The two groups of words were matched for length, frequency and regularity. The lexical agraphic group spelled correctly 94 per cent of the nouns and 93 per cent of the function words. In contrast, the phonological agraphic group spelled correctly 90 per cent of nouns but only 68 per cent of function words. The control subjects were similar to the lexical agraphic group and spelled correctly an equal number of nouns and function words (Table 3).

Spelling Homophonic Words

In order to test the ability of our lexical agraphic patients to incorporate meaning into what they spelled, we gave them a homophone spelling test (Roeltgen *et al.*, 1982*b*). We dictated 41 homophonic words to Cases 1, 2 and 4. Homophones are words with identical phonology but different meaning—the meaning is dependent on the spelling (e.g. sale and sail), not on its phonology. After dictating the homophone, we used it in a sentence and asked the patient to spell the correct homophone. Case 1 spelled correctly an incorrect homophone (e.g. sale instead of sail) on 10 of 41 trials. Case 2 made similar errors on 13 of 41 trials, and Case 4 made similar errors on 7 of 41 trials. Case 3 was not given this test. In order to demonstrate that these patients possessed knowledge of the meanings of these homophones, we also asked them to use the correct homophone in a sentence or provide a definition for it. In this trial the stimulus was presented visually. Cases 1, 2 and 4 correctly defined or used correctly in a sentence 9 of 10, 10 of 13 and 3 of 7 of the homophones for which they had substituted the incorrect homophone (e.g. the response in Case 1 to the task, 'Spell *be*, as in I will *be* there', was 'bee'; when asked to define 'be' after he read it he replied, 'I am . . . I be'). In this study only 3 normal controls were tested with the regular homophones and they were correct on 38, 39 and 40 of 41 trials. Other normal subjects usually spell correctly 97 per cent (approximately 40) of these homophones (Roeltgen *et al.*, 1984).

Reading Nonwords

All patients and control subjects attempted to read the same nonwords that they attempted to spell. All spelling and reading tests involved the same words. In order to minimize any learning effect, the tests were given at different times (with other tests intervening) and at different settings. Ability to read nonwords varied among the patients classified as having lexical agraphia (Table 4). Case 1 was unable to read nonwords but Case 2 read 90 per cent correctly. Cases 3 and 4 had intermediate scores. The patients with phonological agraphia all had difficulty reading nonwords. The normal control subjects read all nonwords correctly.

TABLE 4. READING ABILITY OF INDIVIDUAL PATIENTS

Case No.	*Non-words*	*Regular words*	*Irregular words*	*Difference between reg. and irreg.*	*Nouns*	*Function words*
1	0	64	56	8	80	45
2	90	92	69	23	90	100
3	70	86	83	2	95	95
4	65	86	72	14	95	90
5	65	98	96	2	100	100
6	10	89	84	5	100	88
7	35	96	89	7	100	67
8	45	98	98	0	100	98

Results are expressed as percentage correct.

Reading Regular and Irregular Words

Many of the patients and controls read most regular and irregular words correctly and showed little difference in their ability to read either group (Table 4). Cases 1, 2 and 4 were exceptions to this. Case 1 (who was unable to read nonwords) had a moderate difficulty reading both the regular and irregular words (64 and 56 per cent correct). In contrast, Case 2 (who read nonwords well) read regular words well (92 per cent correct) but had difficulty reading irregular words (69 per cent correct). In addition, an error analysis revealed that many of her errors on irregular words were phonologically correct (e.g. reading morgue as morgūē). Case 4 also made more errors on irregular than regular words but made errors that were usually not phonologically correct. The normal control subject read correctly all the regular and irregular words, and therefore showed no difference in ability to read these two groups of words.

Reading Ambiguous Words

This test was not given because our list of ambiguous words is ambiguous for spelling but not for reading.

Reading Nouns and Function Words

Many of the patients read the nouns and function words almost equally well. Cases 1, 6 and 7, the patients with most difficulty reading nonwords, were the only ones to read nouns better than function words with a difference of greater than 5 per cent. Case 2, who read nonwords well, was the only patient who read function words better than nouns. The normal control subjects read these words flawlessly.

DISCUSSION

Description and Linguistic Analysis of Lexical Agraphia

Analysis of our first 4 patients (Cases 1 to 4) supports the contention that lexical agraphia is a reproducible syndrome. All 4 fulfil the criteria for acquired lexical agraphia on the basis of a focal brain lesion. Each patient had preserved phonological spelling ability as indicated by (1) their preserved ability when spelling nonwords, and (2) the characteristics of their errors; most errors were phonologically correct. Their phonological spelling ability did not differ from that found in brain-damaged or normal control patients ($P > 0.1$ by analysis of variance). The preserved phonological ability of Cases 1 to 4 is in contrast to that found in Cases 5 to 8, who also developed acquired agraphia on the basis of focal brain lesions. This latter group had severely impaired phonological spelling ability as indicated by (1) severely impaired ability when spelling nonwords (differing from Cases 1 to 4 and both control groups, $P < 0.01$ by analysis of variance), and (2) the production of errors that were usually not phonologically correct.

In contrast to their preserved ability to spell nonwords, Cases 1 to 4 had impaired ability to spell irregular words as compared with regular words. The differences ranged from 19 to 39 per cent. The mean difference was 29 per cent and differed from that found in the phonological agraphic group (0 per cent, $P < 0.015$ by t test) and both control groups (7 and 4 per cent, $P < 0.05$ by t test). Previously it has been suggested that irregular words are spelled by a whole word or lexical spelling system that may use a visual word image mechanism (Roeltgen *et al.*, 1983). Therefore decreased ability to spell irregular words with preserved ability to spell nonwords is consistent with disturbed lexical spelling ability, lexical agraphia.

Further evidence that Cases 1 to 4 had impaired lexical spelling ability is evident from the analysis of the results of the ambiguous word test. Although all groups showed a mildly impaired ability to spell words of high ambiguity compared with words of low ambiguity, only Cases 1 to 4 showed a striking difference in this result. This finding is similar to that found in the previously reported patient with lexical agraphia (Beauvois and Dérouesné, 1981).

These results support the hypothesis that lexical and phonological agraphia are two types of linguistic agraphia. The question remains, however, as to whether they are mutually dissociable. An alternative explanation is that phonological agraphia consists of a difficulty in spelling irregular words (lexical agraphia) with a superimposed difficulty spelling nonwords. This explanation is unlikely because patients have been reported with almost isolated disturbances in spelling nonwords (Shallice, 1981; Roeltgen *et al.*, 1982*a*). It therefore appears that the phonological system may be disrupted without interference with the lexical system. The converse, a disrupted lexical system with a preserved phonological system, may also occur. The lexical agraphic patients in this study, especially Case 3 (all nonwords spelled correctly), support this conclusion. This suggests that these systems are mutually dissociable and parallel in operation (fig. 1).

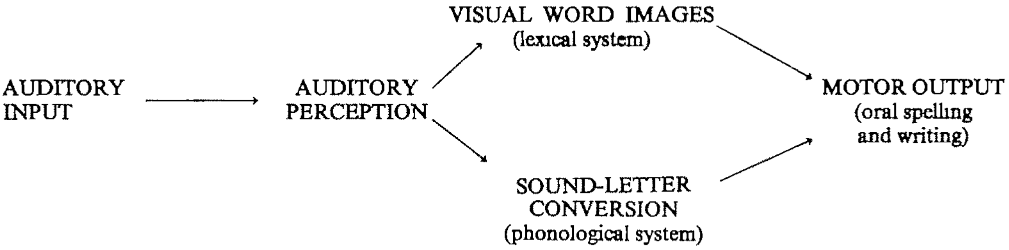

FIG. 1. Diagrammatic model of the two-system spelling hypothesis.

In addition to disrupted lexical with preserved phonological spelling ability, there are two other linguistic features of lexical agraphia. First, there is no apparent effect of word class. Patients with lexical agraphia (Cases 1 to 4) spelled function words correctly (93 per cent) as often as imageable nouns (94 per cent). This pattern is similar to that found in the control subjects. In contrast, the patients with phonological agraphia (Cases 5 to 8) spelled the nouns well (90 per cent correct) but had difficulty with function words (68 per cent correct). This finding has been reported previously in patients with phonological agraphia (Shallice, 1981; Roeltgen *et al.*, 1983).

The second important linguistic feature is the difficulty that the lexical agraphic patients had spelling the correct homophones, a finding previously reported in a patient with probable lexical agraphia (Hatfield and Patterson, 1983). Normal control subjects spell correctly approximately 97 per cent of homophones (with errors being a mixture of incorrect spellings and correctly spelled but incorrect homophones, e.g. sail for sale). The 3 patients with lexical agraphia that were tested frequently spelled correctly an incorrect homophone (Case 1, 24 per cent; Case 2, 32 per cent; Case 4, 17 per cent). These errors were not due to a general lack of knowledge of the homophones' meanings because the patients were usually able to supply the meaning for the word they were unable to spell. The correctly spelled incorrect homophones indicate that some words were spelled despite an inability to use their meanings in written output, and preserved knowledge of the words' meanings. Such a finding suggests at least a partial disruption of the semantic influence on spelling ability. We have previously suggested that the lexical system can be dissociated from semantic influence by destruction of semantic ability or disruption of the pathways by which the semantic area influences spelling ability (Roeltgen *et al.*, 1982*b*). Other studies have shown that semantics may interact with the spelling systems either directly (a in fig. 2) (Brown and McNeill, 1966; Hier and Mohr, 1977; Morton, 1980; Shallice, 1981; Roeltgen, 1983) or indirectly through auditory perception (Wernicke's area) (b, c and d in fig. 2) (Heilman *et al.*, 1976; Heilman *et al.*, 1981). These patients with a disruption of the lexical system have a partial disruption of semantic influence. This indicates that the semantic influence on spelling ability can be diminished by dysfunction of the lexical system in patients with normal semantic ability. This suggests that semantic influence is primarily incorporated into spelling by a direct path from semantics to the lexical system, rather than by an indirect path through auditory word images. If these paths were equal, or if the latter were dominant, semantic influence would not be disturbed by disruption of the lexical system.

The conclusions regarding lexical and phonological agraphia are based on the assumption that these patients have their disabilities on the basis of their acquired cerebral lesions. Alternatively the disabilities could be on the basis of their educational and developmental background. Perhaps patients with lexical agraphia and phonological agraphia differ because of differing educational background or differing premorbid spelling ability. This issue would be best addressed by examining patients before and after their acquired brain lesion. Since this is impractical, we chose to compare our patients with control patients with similar educational background and premorbid spelling ability. Other studies suggest that control subjects with education and spelling ability comparable to the patients described here perform well on all of the tests performed by our patients (Roeltgen *et*

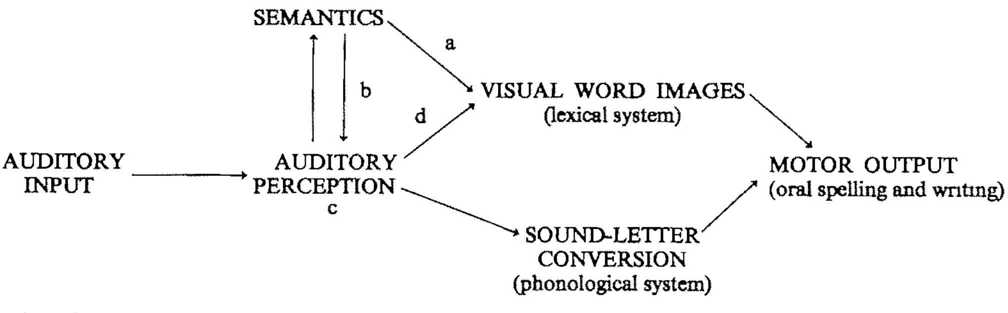

FIG. 2. Diagrammatic model of the two-system spelling hypothesis with the addition of semantic influence Semantic influence on spelling may occur either directly into the lexical system (*a*) or indirectly (*b*, *c*) *via* auditory perception.

al., 1984). Since these matched control subjects do not show disabilities similar to our patients, we can conclude that lexical and phonological agraphia in our patients was probably due to their acquired focal brain lesions.

Although our data suggest that lexical agraphia may occur from acquired brain lesions, they also indicate one problem regarding its time course. All our lexical agraphic patients (Cases 1 to 4) had relatively acute lesions. In contrast, some of the patients with phonological agraphia had chronic and some had acute lesions. Possibly lexical agraphia only occurs in the setting of an acute brain lesion. However, the patient with lexical agraphia described by Beauvois and Dérouesné (1981) had a chronic lesion. This suggests that lexical agraphia like phonological agraphia, may be present in patients with acute and chronic lesions.

Anatomy of Lexical Agraphia

Previous studies have suggested that the anterior inferior supramarginal gyrus (Roeltgen, 1983; Roeltgen *et al.*, 1983) or insula deep to it (Roeltgen *et al.*, 1982*a*) is an important anatomical substrate for phonological agraphia. Analysis of the CT scans from the present group of patients with phonological agraphia (Cases 5 to 8)

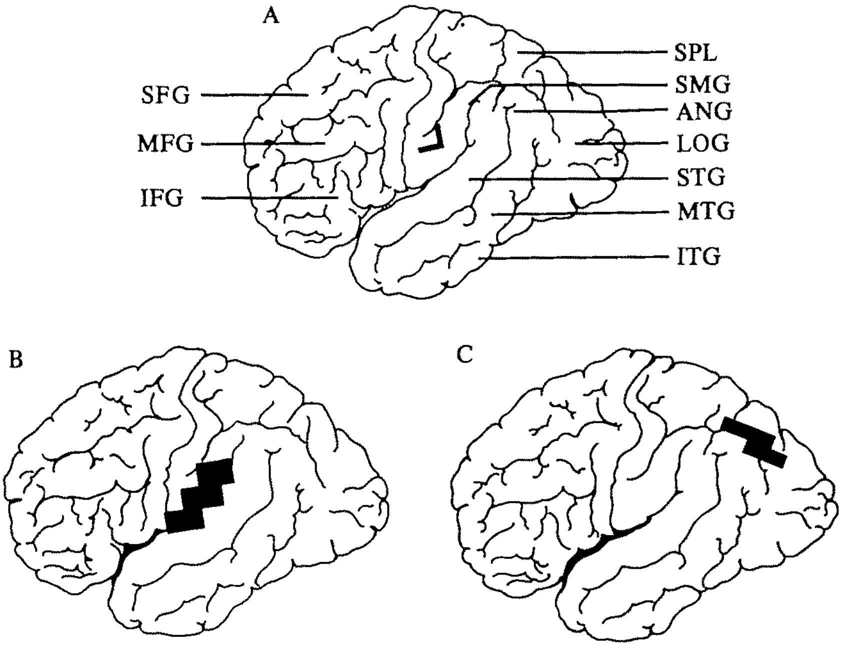

FIG. 3. Summary of CT findings in patients with A, phonological agraphia (present cases), B, phonological agraphia (previously reported cases) and C, lexical agraphia. Lesions were projected onto a lateral view of the left hemisphere and superimposed. Shaded region is site of lesion common to all patients in that group Data in B reprinted with permission from *Neurology, Cleveland*, 33, 755 (1983). SFG = superior frontal gyrus MFG = middle frontal gyrus. IFG = inferior frontal gyrus STG = superior temporal gyrus. MTG = middle temporal gyrus. ITG = inferior temporal gyrus. SPL = superior parietal lobule. SMG = superior marginal gyrus. ANG = angular gyrus. LOG = lateral occipital gyrus.

supports that contention. Fig. 3A shows superimposed CT scans from these patients, the methods employed having been described previously (Roeltgen *et al.*, 1983). The site commonly involved in these patients overlaps the region affected in patients described in a previous study of phonological agraphia (fig. 3B) (Roeltgen *et al.*, 1983). In contrast, the 4 patients with lexical agraphia (Cases 1 to 4) had lesions that overlapped in the region of the posterosuperior angular gyrus and the parieto-occipital lobule (fig. 3C). The lesions of all of the patients with lexical agraphia spared the supramarginal gyrus, the area involved in patients with phonological agraphia. In contrast, the lesions of all of the patients with phonological agraphia spared the angular gyrus. The anatomical descriptions that have accompanied previously reported patients with these disorders are consistent with the lesion location reported here (Beauvois and Dérouesné, 1981; Shallice, 1981; Bub and Kertesz, 1982; Nolan and Caramazza, 1982). Lexical and phonological agraphia therefore appear to be anatomically as well as functionally dissociable. The supramarginal gyrus or insula deep to it appears to be an important anatomical substrate for the production of phonological agraphia. In contrast, the junction of the angular gyrus with the parieto-occipital lobule appears to be an important anatomical substrate for the production of lexical agraphia.

In order to support the contention that these disorders do not occur from *any* focal cerebral lesion but are specific for the sites described above, we tested 4 brain-damaged control patients. These control patients had focal lesions away from the sites implicated to be important for written language. Consistent with this, their spelling ability was almost identical to that of the normal controls. This suggests that lesions only in selected areas cause lexical or phonological agraphia.

The Relationships Among Phonological Agraphia and Dyslexia and Lexical Agraphia and Dyslexia (Surface Dyslexia)

It has been proposed that there are two parallel systems for oral reading, similar to those for spelling (Beauvois and Dérouesné, 1979; Shallice and Warrington, 1980). The phonological reading system is thought to utilize letter to sound conversion and be necessary for reading nonwords. The lexical system is thought to utilize a whole word strategy for accessing phonology without letter to sound conversion, and to be necessary for reading irregular words. Disruption of the former system has been termed phonological dyslexia (alexia). Disruption of the latter has been termed surface dyslexia (lexical alexia).

At least two hypotheses have been proposed regarding the relationships of phonological reading and spelling. The first suggests that both phonological agraphia and alexia result from disruption of the same basic phonological system (Nolan and Caramazza, 1982). Alternatively it has been proposed that there are separable phonological systems for reading and spelling and that they may be disrupted independently (Beauvois and Dérouesné, 1981; Shallice, 1981; Roeltgen *et al.*, 1983). Similarly there are at least two possible hypotheses for the relationships between the lexical systems of reading and spelling. Reading and spelling may be subserved by a generalized lexical system or there may be two independent lexical systems, one for reading and one for spelling.

Phonological agraphia has previously been reported with phonological alexia (Shallice, 1981; Nolan and Caramazza, 1982; Roeltgen *et al.*, 1983), lexical alexia (Roeltgen *et al.*, 1983; Sevush *et al.*, 1983) and with no alexia (Roeltgen *et al.*, 1982*a*). All patients with phonological agraphia in the present study (Cases 5 to 8) had some difficulty reading nonwords and therefore had some degree of phonological alexia (Table 4).

The one previously reported patient with lexical agraphia had phonological alexia (Beauvois and Dérouesné, 1981). Case 1 in this study is similar in that, although he spelled correctly 90 per cent of nonwords, he was unable to read correctly any of these same nonwords (Tables 2 and 4). In addition, he spelled correctly only 28 per cent of the irregular words but read correctly 56 per cent of the same irregular words. When reading, he showed a word class effect, reading correctly 80 per cent of nouns and 45 per cent of function words. This finding is frequently seen in phonological alexia.

In contrast to Case 1, Case 2 spelled and read correctly 90 per cent of the nonwords. The relationship between her ability to spell and read regular and irregular words was also similar. When spelling, she was correct on 19 per cent more regular than irregular words, and when reading, she was correct on 23 per cent more. She did not show a word class effect for either modality. She therefore appeared to have lexical agraphia and lexical alexia (surface dyslexia).

These findings indicate that the syndromes of phonological agraphia and phonological alexia as well as lexical agraphia and lexical alexia are all dissociable. Such dissociations support the second hypothesis, that individual systems subserve the four processes (phonological spelling and reading and lexical spelling and reading).

ACKNOWLEDGEMENTS

The authors thank Dr S. Streufert for help with statistical analysis and Cindy Cover in the preparation of the manuscript. Informed consent was obtained from the control subjects in this study.

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(*Received August 2, 1983. Revised November 29, 1983*)

APPENDIX

Irregular words

1. menace
2. mischief
3. sovereign
4. weapon
5. prestige
6. yacht
7. trouble
8. daybreak
9. shoes
10. prairie
11. palace
12. cuisine
13. edifice
14. beverage
15. morgue
16. kerchief
17. comrade
18. meadow
19. leopard
20. friend
21. honour
22. hostage
23. glacier
24. epistle
25. shriek
26. advantage
27. engine
28. tomb
29. circuit
30. village
31. chief
32. death
33. heaven
34. jealousy
35. health
36. answer
37. thought
38. dress
39. pleasure
40. limb
41. earth
42. ritual
43. marriage
44. justice
45. building

Regular words

1. settler
2. winter
3. mucus
4. madness
5. insect
6. abdomen
7. lobster
8. tidbit
9. newspaper
10. blister
11. prosperity
12. library
13. henchman
14. garden
15. blandness
16. harness
17. sunset
18. loyalty
19. victim
20. bravery
21. effort
22. nutmeg
23. flask
24. fabric
25. bandit
26. moment
27. green
28. interest
29. freedom
30. frog
31. dress
32. history
33. reflex
34. contract
35. master
36. hardship
37. attitude
38. cash
39. corner
40. sadness
41. hotel
42. speech
43. letter
44. bottle
45. industry

Ambiguous words

Low ambiguity

1. hotel
2. butter
3. letter
4. event
5. charm
6. paper
7. gold
8. flesh
9. winter
10. string

Medium ambiguity

1. brain
2. temple
3. artist
4. speech
5. corner
6. army
7. blood
8. chief
9. breast
10. anger

High ambiguity

1. city
2. crime
3. ocean
4. queen
5. apple
6. breeze
7. advice
8. wheat
9. church
10. cotton

These words are part of the 'Battery of Linguistic Analysis for Writing and Reading' (Roeltgen *et al*, 1984)

Brain (1984), **107**, 829–854

CATEGORY SPECIFIC SEMANTIC IMPAIRMENTS

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SUMMARY

We report a quantitative investigation of the visual identification and auditory comprehension deficits of 4 patients who had made a partial recovery from herpes simplex encephalitis. Clinical observations had suggested the selective impairment and selective preservation of certain categories of visual stimuli. In all 4 patients a significant discrepancy between their ability to identify inanimate objects and inability to identify living things and foods was demonstrated. In 2 patients it was possible to compare visual and verbal modalities and the same pattern of dissociation was observed in both. For 1 patient, comprehension of abstract words was significantly superior to comprehension of concrete words. Consistency of responses was recorded within a modality in contrast to a much lesser degree of consistency between modalities. We interpret our findings in terms of category specificity in the organization of meaning systems that are also modality specific semantic systems.

INTRODUCTION

Neuropsychological and neurological data provide an important source of evidence on the cerebral organization of visual perception, in identifying not only the component processes in the attainment of a meaningful percept, but also the categories into which meaningful percepts are to be classified. It is now generally accepted that a failure of visual identification that cannot be accounted for by impaired sensory processes (or other confounding factors) can occur as a selective deficit. Not only can visual agnosic deficits at the level of perceptual analysis—apperceptive agnosia—be distinguished from those of semantic analysis—associative agnosia—there is also evidence of differentiation at a semantic level. Thus visual agnosia for objects, colours, faces, topography, parts of the body, letters and numbers have all been identified as mutually dissociable deficits and hence it can be inferred that the neural substrates of these categories are also different (*see* Hécaen and Albert, 1978).

There have been pointers to suggest that such classification might be taken a stage further and that a more fine grain categorical organization can be observed within the broad category of visual object agnosia. As yet the evidence is sparse and mainly anecdotal. Nielson (1946) described a patient (C.H.C.) who he claimed had considerably greater difficulty in identifying inanimate objects by sight or touch, and foods except by taste, than in identifying all living things (including flowers). He also observed the converse pattern of deficits in a patient (Flora D) who had greater difficulty in identifying 'animate objects' than inanimate objects. Hécaen and de Ajuriaguerra (1956) reported a single case study of a patient with a left hemisphere lesion in whom they observed a category specific visual agnosia; identification of inanimate objects was more impaired than identification of animals. Konorski (1967) extrapolated from such dissociations between cognitive deficits, to distinguish nine 'gnostic fields', one of which was living things. He also speculated that small manipulable objects form a separate category from nonmanipulable objects. More recently Warrington (1981) provided quantitative evidence of a patient (C.A.V.) who had a significantly greater impairment in the identification of the visual representation of concrete concepts as compared with abstract concepts using a word/picture matching test (T. Shallice and J. McGill, unpublished) in which the abstract words were represented by pictures of concrete objects (e.g. *aptitude*—man playing a bassoon) of approximately equivalent familiarity and complexity as the pictures representing concrete concepts (e.g. a *donkey*). The evidence for category specific deficits is more firmly established for auditory-verbal than visual information. Impaired comprehension of colour names and body part names has long been recorded in the neurological literature. Indeed Goodglass *et al.* (1966), in the first quantitative investigation of semantic word categories, concluded that the selective impairment or preservation of semantic categories occurred not infrequently in an aphasic population. In a single case study Warrington (1975) demonstrated a significantly greater auditory comprehension impairment for concrete words than abstract words and more recently, quantitative evidence of the selective impairment of the comprehension of inanimate object names has been reported (Warrington and McCarthy, 1983).

Category specificity, then, has been documented in both the visual and verbal domains, but the relationship between the two is rarely considered. Typically visual object agnosia is viewed only from the perspective of visual processing. Yet the relationship between visual 'semantics' (i.e. knowledge of things), and their verbal equivalent, could well have far reaching theoretical implications. It seems fairly certain that there is not a one to one correspondence between one domain and the other. For instance, it is accepted (and it has occasionally been documented) that verbal comprehension can be intact in patients with a visual object agnosia (Rubens and Benson, 1971; Hécaen *et al.*, 1974). Conversely, patients with word comprehension difficulties—transcortical sensory aphasia—are not necessarily agnosic for visual stimuli (Benson, 1979; Warrington and McCarthy, 1983).

Such observations have usually been interpreted in terms of a unitary semantic system that has been specifically disconnected from 'lower level' modality specific perceptual systems (Geschwind, 1965). There are, however, a number of agnosic phenomena which are difficult to interpret in terms of a single semantic system disconnected from particular input modalities, and more easily interpreted in terms of modality specific semantic systems. Thus certain semantic memory impairments leave the patient with a stable but impoverished semantic processing ability. Only a limited set of items can be identified and for other items, at best, only superordinate information is retained (Warrington, 1975; Coughlan and Warrington, 1981). Such a pattern of impairment can occur together with lack of concordance between modalities; it is then most easily accounted for in terms of the degradation of the stored information within two semantic systems rather than a disconnection. Moreover other observations also suggest the existence of independent modality specific semantic systems. Beauvois *et al.* (1978) have argued that the observations of patients with optic aphasia and tactile aphasia indicate that separate semantic systems for verbal, visual and tactile information exist (*see also* Beauvois, 1982).

In this paper we report 4 patients recovering from a herpes simplex encephalitis in whom clinical observations suggested the selective preservation of the identification of inanimate objects. Our aim in these investigations was to obtain further evidence for the categorical organization and modality specificity of semantic systems.

CASE HISTORIES

Case 1

J.B.R., a 23-year-old electronics undergraduate, was admitted to the National Hospital on January 24, 1980 Two days previously he had had a grand mal seizure following which he became progressively drowsy. On examination he was pyrexial, his neck was stiff and Kernigs' sign was positive. He was confused and disorientated. EEG showed repetitive complexes bilaterally and a CT scan showed widespread low attenuation, maximal in both temporal lobes, that was considered consistent with herpes simplex encephalitis (*see* fig.). He gradually became more active and alert but he remained very confused and for a period of one week, three weeks after the onset of his illness, he was observed to eat and drink indiscriminately, including nonfood items. He continued to improve slowly and by August 1980 there were no neurological signs of note other than the cognitive deficits described below (a detailed neurological account of this patient has been given by Greenwood *et al.*, 1983).

Psychological test findings. J.B.R.'s scores on intelligence tests are given in Table 1. He was totally disorientated in time and place and he was densely amnesic for ongoing events and for events prior to his illness. On recognition memory tests for words and faces he scored at a chance level (Table 1). He was unable to identify contemporary famous faces or names. His perceptual skills were considered

TABLE 1 COGNITIVE TEST RESULTS

	J B R		S B.Y.	K.B	I.N G
	14 4 80	7 8.80	28.6 80	28.4.81	11 6 82
Verbal IQ	102	101	95	70	70
Performance IQ	78	103	93	76	58
Arithmetic	12	15	9	4	4
Similarities	11	10	7	3	6
Digit Span	9	7	7	7	6
Vocabulary	9	8	12	3	4
Picture Completion	7	8	7	6	2
Block Design	9	11	10	5	6
Picture Arrangement	4	7	5	6	0
Matrices IQ	99	100	NT	90	70
Recognition Memory					
Words (n = 50)	29	—	29	NT	23
Faces (n = 50)	30	—	18	27	25

Performance on WAIS, Matrices and Warrington's (1984) Recognition Memory Tests.

to be intact (e.g. on the Warrington and Taylor (1978) test of matching usual and unusual view photographs he scored 20/20 correct and 19/20 correct on the Warrington and James (1967) fragmented letter test). His spontaneous speech was fluent although he used a somewhat limited and repetitive vocabulary; occasional word-finding difficulty was noted and he tended to use circumlocutory expressions. Articulation, phrase length and syntax were considered to be normal. His score on the modified Token Test (Coughlan and Warrington, 1978) was satisfactory (15/15). He failed to score on a graded difficulty naming test (GNT) (McKenna and Warrington, 1983) and on a test of naming common objects he scored 11/15 (Coughlan and Warrington, 1978). He failed to score on the NART (Nelson, 1982) and on the Schonell reading test he made dyslexic errors (regularizations) with the lower frequency irregularly spelt words. He had no difficulty in naming or identifying colours, shapes and letters. However, his ability to identify inanimate objects by sight or by touch was impaired and he appeared to have more difficulty in identifying pictures of animals than pictures of inanimate objects and in comprehending animal names than object names. He performed at a very defective level on the Peabody Picture Vocabulary Test (score 26). Similarly on the Shallice and McGill Concrete/Abstract Picture Word Matching Test his comprehension of both categories of word was severely impaired (*see* Table 2).

TABLE 2 CONCRETE/ABSTRACT WORD/PICTURE MATCHING

	Concrete *n* = *30*	*Abstract* *n* = *30*
J.B.R. (7.4.80)	14	19
S.B.Y. (28.6 82)	15	11
L. hemisphere lesion group	1 6	7.6

Error scores for J.B.R. and S.B.Y. and the mean error score for a consecutive series of patients with left hemisphere lesions ($n = 45$) (chance = 22 5).

In summary, J.B.R. was able to function at an overall average level on tests of intelligence. He was densely amnesic. His language skills, especially his spontaneous speech, were relatively intact. He had significant difficulties, however, both with visual identification and word comprehension.

Case 2

S.B.Y., a 48-year-old naval officer (engineer), was admitted to a private hospital in Hong Kong on February 15, 1982. He was febrile and confused. He became comatose and was treated with cytosine arabinoside and dexamethasone. A CT scan was normal but there was a raised protein content in the CSF. His level of consciousness gradually returned to normal and on May 7, 1982 he was transferred to the Queen Elizabeth Military Hospital, Woolwich. On examination there were no neurological signs other than the cognitive deficits described below. A repeat CT scan in May 1982 showed areas of low attenuation in both temporal lobes that were considered to be compatible with the diagnosis herpes simplex encephalitis (*see* fig.).

Psychological test findings. S.B.Y.'s intelligence test results are given in Table 1. He was almost totally disorientated in time and place and his memory for ongoing events was very impaired. He scored at a chance level on recognition memory tests for words and faces. His perceptual skills appeared to be intact insofar as he made no errors on the fragmented letters test and on matching usual and unusual view objects. His spontaneous speech was very fluent and apart from a tendency to repeat himself, only occasional word-finding difficulties were noted. His phrase length, syntax and articulation appeared to be entirely normal. His performance on the modified Token Test was very satisfactory (15/15). However, his comprehension of individual words appeared to be impaired and on tests of object naming his performance was very poor (GNT 0/30) as was naming from description (1/15) (Coughlan and Warrington, 1978). He was still able to identify and name colours and letters and he was able to read at a high average level (NART 31/50). Identification of inanimate objects by sight and by touch was impaired and he appeared to have more difficulty with animal and food names than object names. His performance on the Peabody Picture Vocabulary Test was very weak (score 73). On the Shallice and McGill Concrete/Abstract Picture Matching Task, although his score was only slightly weak compared with patient controls for the abstract words, it was very significantly impaired for the concrete words (Table 2).

In summary S.B.Y.'s overall level on intelligence tests was just within the average range. It is assumed that he would have been able to function at least within the high average range premorbidly and that these scores indicate some generalized intellectual deterioration. In addition he had a dense amnesic syndrome, a visual identification deficit and impaired word comprehension.

Case 3

K.B., a 60-year-old housewife, was admitted to the National Hospital on April 27, 1981 for further assessment of her cognitive deficits following a herpes simplex encephalitis diagnosed in June 1979. During the acute illness she developed a frontal headache, fever and increasing confusion over a 48 h period. During the early stages of recovery she was reported to be very amnesic, dysphasic and agnosic. She was also observed to eat food and nonfood items indiscriminately.

On examination there were no neurological signs of note other than cognitive dysfunctions (described *below*). An EEG was normal. A CT scan showed marked residual low attenuation bitemporally most marked on the left (*see* fig.). (A detailed neurological account of this patient has been given by Greenwood *et al.*, 1983.)

Psychological test findings. Intelligence test results are given in Table 1. She was completely disorientated for time and place and appeared to be almost totally unable to recall or recognize ongoing events. On a recognition memory test for faces she scored at a chance level. Her spontaneous speech was very sparse as to word choice and word-finding difficulties were very evident. On the Boston Diagnostic Aphasia Battery the pattern of deficit was that of a global dysphasic with articulation spared. She was only able to name 1/15 common objects and she failed to score on a test of naming from description. Her performance on the Peabody Picture Vocabulary Test was extremely poor (score 26). It was noted that she was unable to name or identify objects by touch. She was fairly accurate in identifying and naming letters, actions, body part names and colours. Her reading and spelling were impaired (she failed to score on the NART). In the course of clinical assessment it was observed that K.B. had more difficulty in identifying animals and foods than inanimate objects and a similar pattern of difficulty was observed for her word comprehension.

Case 4

I.N.G., a right-handed housewife aged 44 years, was admitted to the National Hospital between June 10 and 27, 1982 for assessment of her suitability for rehabilitation. A herpes simplex encephalitis had been diagnosed in November 1978 on the basis of a three day history of vomiting, pyrexia and seizures. A CT scan then showed a low attenuation lesion deep in the right hemisphere and a brain biopsy demonstrated necrotic tissue. At the time of her discharge in June 1979 she was severely amnesic, aphasic and agnosic and she had been observed to attempt to eat nonfood items. She was still incontinent and continued to have generalized seizures which were preceded by left-sided clumsiness and turning of her head to the right. On admission to the National Hospital, neurological examination was normal apart from higher cerebral function deficits. A repeat CT scan showed areas of bilateral temporal low attenuation and marked atrophy which were considered consistent with her known herpes encephalitis (*see* fig.).

Psychological test findings. Intelligence test results are given in Table 1. She was disorientated in time and place and was completely unable to recall or recognize ongoing events or hospital personnel. On recognition memory tests for words and faces she scored at a chance level (Table 1). Her spontaneous

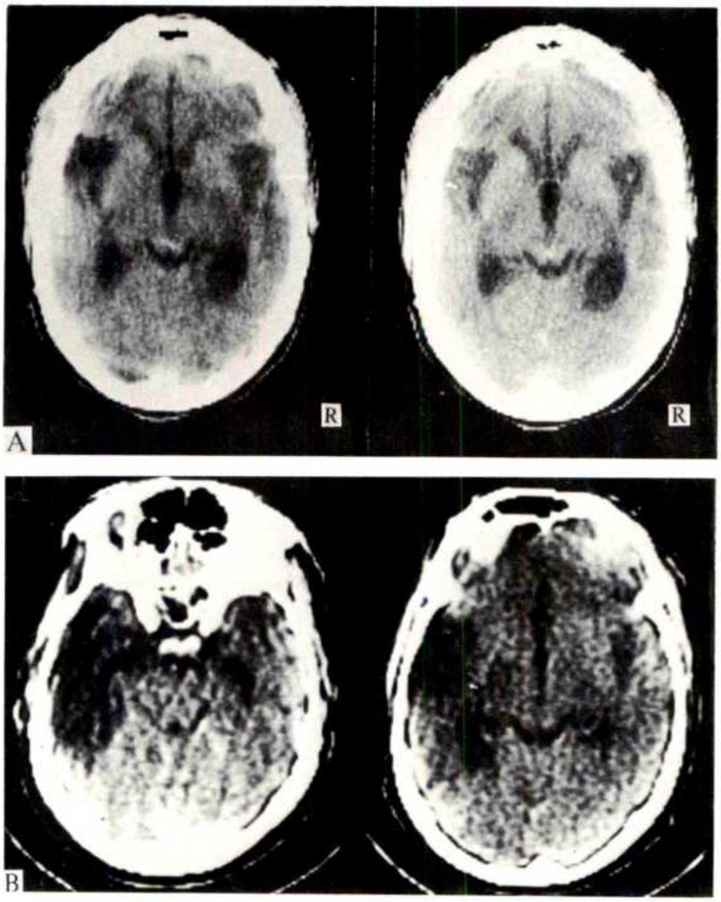


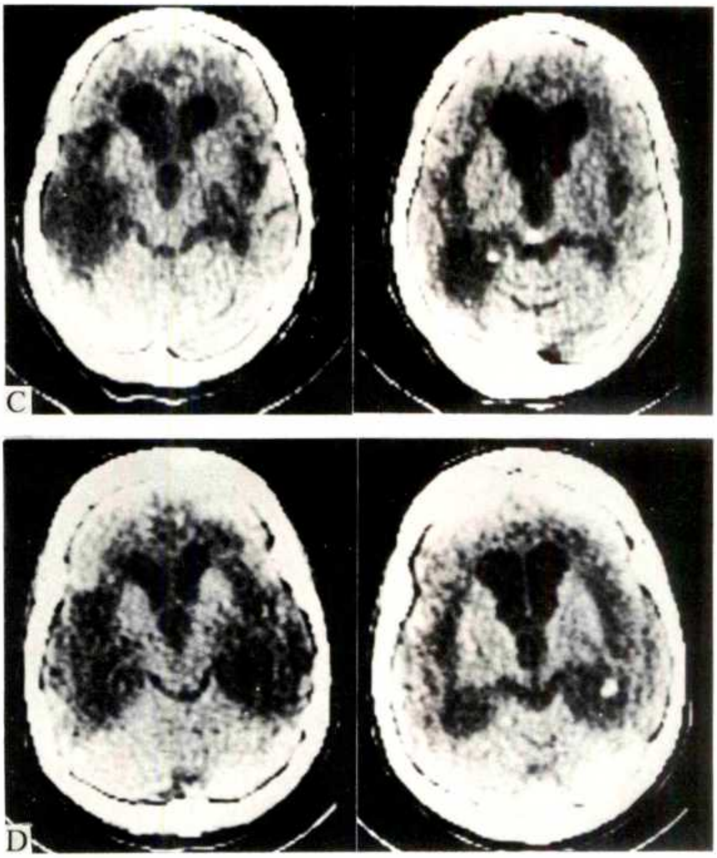
FIG. CT scans of A, J.B.R. (October 1980). B, S.B.Y. (May 1982). C, B.A.R. (April 1981) and D, I.N.G. (June 1982).

speech was exceptionally sparse; she tended to repeat automatic phrases and very rarely attempted propositional speech. Within these limitations her phrase length, syntax and articulation appeared to be normal. Her performance on object naming tests was very impaired (e.g. 5/15 common objects correct) as was her performance on the modified Token Test (9/15). However, she could name the primary colours and common shapes. Her reading and spelling skills were extremely defective. Her ability to identify common inanimate objects by sight or touch was impaired and she appeared to have even greater difficulty in identifying foods and animals. She performed at a very defective level on the Peabody Picture Vocabulary Test (score 44). I.N.G. was very distractable in the test situation and it was somewhat difficult to hold her attention for sufficient time to complete tests without interruption.

In summary, there was evidence of a fairly marked degree of generalized intellectual impairment. In addition she was markedly amnesic, dysphasic, dyslexic, dysgraphic and agnosic.

Summary of Case Reports

These 4 patients were at various stages of recovery from a herpes simplex encephalitis. The clinical course of their illness, the neurological findings and the residual cognitive deficits were qualitatively



similar in the 4 cases. CT scans demonstrated predominantly bitemporal damage in all 4 patients. In addition to varying degrees of dementia and expressive speech functions, these patients all had a severe global amnesic syndrome and a comprehension deficit which encompassed both visual and verbal knowledge. In all 4 cases clinical observation suggested that within the domain of 'concrete' concepts, knowledge of inanimate objects was spared relative to knowledge of living things and food. Their residual comprehension capacities were documented in more detail.

EXPERIMENTAL INVESTIGATIONS

Difficulties in visual identification had been observed in all 4 patients on clinical assessment and in addition difficulties in verbal comprehension were apparent. Our aim in this series of experiments was to document and explore these impairments and in particular, to consider the possible categorical specificity of their deficits and the correspondence between the visual and verbal deficit. The main clinical difference between these 4 patients was in their expressive speech capacities. Neither K.B. nor I.N.G. were able to give coherent word definitions or verbal descriptions of pictures and they were therefore tested in one experiment only (Experiment 8) in which a matching to sample technique was adopted. J.B.R. and S.B.Y. were both able to express themselves fairly lucidly and fluently within the constraints imposed by their impoverished verbal vocabulary. It was therefore possible to investigate their comprehension capacities in much more detail using picture description and word definition tasks (Experiments 1–7).

In these experiments each verbal response was scored correct or incorrect by three independent judges and the analyses were based on the consensus rating. A lenient scoring criterion was adopted, the judges being instructed to accept as correct 'reasonable evidence that the core concept is conveyed'. In addition they were required (1) to make allowance for dysphasic word-finding difficulties, (2) to credit any correct homonym, (3) to ignore the evidence of gesture, (4) not to give credit for superordinate information alone, (5) to ignore verbal description of features present in a picture (e.g. tail, legs) and (6), in the case of picture description, identification was assumed to be correct if the stimulus was correctly named.

Experiment 1: Identification of Visual and Verbal Stimuli

Our aim in this experiment was to document the relative severity and concordance of J.B.R. and S.B.Y.'s impaired identification of visual and verbal stimuli. The test stimuli consisted of 40 clear line drawings (mostly of inanimate objects) selected from the Zinkin and Birtchnell set (1968). All items were well within the visual/verbal vocabulary of the average adult. The patients first attempted to identify the pictures by naming or description. After each response, irrespective of quality, the patient was asked to elaborate *once*. After a short interval the patients attempted to define the object names presented auditorially. S.B.Y. attempted this task a second time ten days later and J.B.R. was retested on the visual version only, a second time, later on the same day.

The percentage of responses judged correct for the visual and verbal version of this task for each patient, together with the number of visual stimuli correctly named, is given in Table 3. There was a small but insignificant advantage of auditory presentation for both patients (McNemar test $P > 0.2$ for all comparisons).

In this and succeeding experiments stability in performance over repeated testing was assessed using the contingency coefficient (Siegel, 1956) with the proviso that

TABLE 3. EXPERIMENT 1.
IDENTIFICATION OF VISUAL AND VERBAL STIMULI

	Visual	*Auditory*
J.B.R.		
(20.6.80)	68	78
(20.6.80)	68	NT
S.B.Y.		
(28.6.82)	50	53
(6.7.82)	48	55

Percentage correct for each presentation condition on each occasion.

performance for both sets of data lay between 20 and 80 per cent (this avoids artefacts arising from floor and ceiling effects). Comparing responses within a modality, for J.B.R. there was a significant degree of consistency between the two sets of responses in the visual modality ($C = 0.61, P < 0.001$) and S.B.Y. showed the same consistency effect in both modalities (visual, $C = 0.48$, $P < 0.001$; verbal, $C = 0.33$, $P < 0.05$). It should be noted that the maximum value for a 2×2 contingency coefficient (C) is 0.71. By contrast, the pattern of consistency scores between modalities was on the whole weaker. For J.B.R. there was an insignificant degree of consistency between his ability to identify an item presented visually and the same item presented auditorially ($C = 0.26, P > 0.05$). This was also the case for S.B.Y. on the first test session ($C = 0.15, P > 0.2$); on the second occasion, however, there was a significant degree of concordance ($C = 0.49, P > 0.01$).

Performance on this simple task would be expected to be at ceiling level in any normal average adult. Given the patients relatively intact expressive speech, the high error rate observed on both the visual and verbal version of this task provides quantitative evidence of a moderately severe visual and verbal agnosia in both patients (very comparable in severity to the patients reported by Warrington, 1975).

Experiment 2: Identification of Inanimate Objects and Living Things

It had been observed that the ability of these patients to identify certain categories of both picture stimuli and 'concrete' words, namely, animals and plants, was particularly poor whereas inanimate objects appeared to be relatively spared. The aim of this experiment was to explore the possibility of a category specific identification deficit for both visual and verbal stimuli.

The test stimuli consisted of 96 coloured pictures: 48 animals and plants and 48 inanimate objects. The two sets did not differ significantly in spoken word frequency (*see* Appendix). J.B.R. and S.B.Y. first attempted to identify by naming or describing each stimulus picture, alternating between the two major categories. Secondly, they attempted to define each picture name, presented in the same order, auditorially.

The percentage correct for each category for each mode of presentation for each patient is given in Table 4. For both J.B.R. and S.B.Y. there was a striking discrepancy between their ability to identify inanimate objects either with pictures or words and their inability to identify living things. J.B.R. was almost at ceiling level on the visual inanimate object condition, yet he virtually failed to score on the visual living things condition. It was also shown that his ability to name objects that he succeeded in identifying was relatively well preserved and far superior to his ability to name living things; but this was not the case for S.B.Y. whose naming skills were very impaired (*see* Table 4). Although S.B.Y.'s overall level was somewhat worse than J.B.R.'s both patients were usually able to identify the superordinate category with auditory presentation (*see* Table 4). The small difference in favour of picture identification compared with name definition for

TABLE 4. EXPERIMENT 2 IDENTIFICATION OF PICTURES, NAMES, LIVING THINGS AND INANIMATE OBJECTS

	Living things				*Inanimate objects*			
	Visual		*Auditory*		*Visual*		*Auditory*	
	Identified	*Named*	*Identified*	*Superordinate*	*Identified*	*Named*	*Identified*	*Superordinate*
J.B.R. (5.8.80)	6	6	8	90	90	67	79	94
S.B.Y. (27.7.82)	0	0	0	75	75	0	52	85

Percentage correct identification score, naming score and superordinate score.

inanimate objects was significant for S.B.Y. (McNemar test A = 16, D = 5, $P < 0.05$) but not for J.B.R. (McNemar test A = 9, D = 4, $P > 0.1$).

Qualitatively the difference between the major categories was very striking. Some examples of their responses to the inanimate object words were as follows.

J.B.R. Tent—temporary outhouse, living home.
Briefcase—small case used by students to carry papers.
Compass—tools for telling direction you are going.
Torch—hand-held light.
Dustbin—bin for putting rubbish in.

S.B.Y. Wheelbarrow—object used by people to take material about.
Towel—material used to dry people.
Pram—used to carry people, with wheels and thing to sit on.
Submarine—ship that goes underneath sea.
Umbrella—object used to protect you from water that comes.

In contrast some examples of their responses to living things were as follows.

J.B.R. Parrot—don't know.
Daffodil—plant
Snail—an insect animal.
Eel—not well.
Ostrich—unusual.

S.B.Y. Duck—an animal.
Wasp—bird that flies.
Crocus—rubbish material.
Holly—what you drink.
Spider—person looking for things, he was a spider for a nation or country.

As there were both floor and ceiling effects it was only possible to compute the concordance of visual and auditory presentation for S.B.Y.'s responses to the inanimate objects category. The contingency coefficient was not significant (C = 0.12, $P > 0.2$).

Experiment 3: Definition of Names of Living Things and Inanimate Objects

In the previous experiments we documented a particularly striking dissociation of the ability to identify pictures and names of inanimate objects compared with pictures and names of living things. Our aim in this experiment was to assess the reliability of these observations by using a completely different set of words.

The test items consisted of names of 40 living things (animals and plants) and 40 inanimate objects matched for frequency. J.B.R. was required to define each name, alternating between the two major categories. This task was attempted twice on the same day (June 20, 1980). S.B.Y. did not attempt this task.

TABLE 5 EXPERIMENT 3. IDENTIFICATION OF NAMES OF LIVING THINGS AND INANIMATE OBJECTS

Living things				*Inanimate objects*			
1st attempt		*2nd attempt*		*1st attempt*		*2nd attempt*	
Identified	*Superordinate*	*Identified*	*Superordinate*	*Identified*	*Superordinate*	*Identified*	*Superordinate*
15	50	10	63	85	93	75	93

Percentage correct identification score and superordinate score for J.B.R.

The percentage correct score for each category for each mode of presentation is given in Table 5. Again there is a very striking discrepancy in the quality of his responses to stimuli in the two categories. Of the living things, he identified only a very few of the high frequency items and was able to indicate the superordinate category for approximately half the stimuli. Identification for most of the inanimate objects was remarkably good and he almost always knew the superordinate category (*see* Table 5). His ability to indicate the superordinate for the inanimate object category was significantly better than for living things ((i)$\chi^2 = 17.64$, $P < 0.01$; (ii) $\chi^2 = 10.32$, $P < 0.01$). Our findings in this experiment replicate the verbal condition of Experiment 2. Consistency measures could not be computed because of the floor and ceiling effects.

Experiment 4: Identification of Foods and Inanimate Objects

In addition to the selective impairment in the identification of living things, it had been observed that J.B.R.'s comprehension of food names appeared to be very poor. The aim of this experiment was to compare his ability to identify pictures and names of foods and inanimate objects. S.B.Y. was not tested on this experiment.

The test stimuli consisted of 30 coloured pictures of foods and 30 coloured pictures of inanimate objects (*see* Appendix). J.B.R. first attempted to identify each picture by naming or description, the foods and the inanimate object items being alternated. He then attempted to identify each food and object name. The percentage correct for each category for each presentation mode together with his naming and superordinate identification score is given in Table 6. Some days later he attempted to mime an action appropriate to 20 foods and 20 inanimate objects (e.g. banana, spaghetti—actual object presented) that partially overlapped with those items previously used. His miming performance was scored jointly by T.S. and E.K.W.

TABLE 6. EXPERIMENT 4. IDENTIFICATION OF FOODS AND INANIMATE OBJECTS

Foods				*Inanimate objects*			
Visual		*Auditory*		*Visual*		*Auditory*	
Identified	*Named*	*Identified*	*Superordinate*	*Identified*	*Named*	*Identified*	*Superordinate*
20	20	30	93	87	40	77	87

Percentage correct identification score, naming score and superordinate score for J.B.R.

His score was 20 per cent correct for foods and 65 per cent correct for inanimate objects. His ability to identify inanimate objects for both modes of presentation is significantly better than his ability to identify foods (visual $\chi^2 = 26.8$, $P < 0.001$, 1 d.f.; verbal $\chi^2 = 13.1$, $P < 0.001$, 1 d.f.) and an identical pattern of scores was obtained on the mime condition ($\chi^2 = 8.29$, $P < 0.01$, 1 d.f.). The miming result provides further evidence that this category specific impairment cannot be attributed to any difficulty of expression, eliminating the possibility that food stimuli are more difficult to describe than inanimate object stimuli. In this experiment we have obtained as striking a dissociation between identification of food and inanimate objects as was obtained for living things and inanimate objects in the previous two experiments. Consistency measures could not be computed because of floor and ceiling effects.

Experiment 5: Identification of Animate, Inanimate Objects and Foods

A problem in comparing categories in the visual mode is that items may differ in familiarity just as words do in their frequency of usage. Although word frequency counts are available for all test stimuli used in these experiments, this may not be an adequate control for visual familiarity. The Snodgrass and Vanderwart (1980) stimuli were specifically standardized to provide visual familiarity ratings and were thus considered particularly suitable for investigating both category and mode of presentation effects.

The test stimuli consisted of a subset of the Snodgrass and Vanderwart drawings: 40 animals, 40 inanimate objects and 20 foods. S.B.Y. (July 27, 1982) first attempted to name or identify each of the 100 drawings, presented in pseudorandom order. Secondly, he attempted to identify each stimulus name (these stimuli were not available to us at the time we tested J.B.R.). The percentage correct scores for each category for each mode of presentation are given in Table 7.

TABLE 7 EXPERIMENT 5 SNODGRASS AND VANDERWART PICTURES TEST

Animals		*Foods*		*Inanimate objects*	
Visual	*Auditory*	*Visual*	*Auditory*	*Visual*	*Auditory*
13	10	25	25	60	65

Percentage correct for each category for each mode of presentation for S.B.Y.

For both types of stimuli an analysis of covariance using the linear logistic model was performed. For the visual results there was a highly significant effect of category ($\chi^2 = 17.5$, $P < 0.001$, 2 d.f.) with inanimate objects being identified significantly better than both animals ($z = 3.3$, $P < 0.001$) and food ($z = 2.65$, $P < 0.01$); there was no significant difference between animal and food categories ($z = 0.41$, $P > 0.3$). For the auditory modality the results were very similar; there was an overall effect of category ($\chi^2 = 23.2$, $P < 0.001$, 2 d.f.) with inanimate objects being identified better than both animals ($z = 3.64$, $P < 0.01$) and foods ($z = 3.13$, $P < 0.001$) with no difference between comprehension of animal and food names ($z = 0.41$, $P > 0.3$).

The consistency of his visual and verbal responses for the inanimate objects category for the two presentation modes was computed: the contingency coefficient was insignificant ($C = 0.04$, $P > 0.5$).

In this experiment we have taken into account not only word frequency but also visual familiarity and clear evidence of significant category effects is still obtained. The lack of concordance between the two modes of presentation is again a feature of the data.

Experiment 6: Abstract and Concrete Word Comprehension

In the previous experiments three specific categories were explored and evidence for category specific deficits within the 'concrete' domain were documented for both a visual and auditory mode of presentation. Identification of living things and foods appeared to be selectively impaired. Our aim in this experiment was to explore the ability of J.B.R. and S.B.Y. to comprehend a wider range of verbal stimuli that spanned the full abstract/concrete range.

The test stimuli consisted of two subsets of the Brown and Ure (1969) word list. J.B.R. attempted to define 323 words of which 132 were of AA and A frequency, the remaining 191 were in the frequency range 1 to 50. Half of the total pool had a concreteness rating above the median value of 4.47. S.B.Y. attempted to define 190 words of which 50 were A or AA frequency and 140 in the 1 to 50 frequency range; half of each frequency range had a concreteness rating above the median. In order to ensure correct perception of each word the patients were asked to repeat it correctly before attempting a definition.

The percentage correct for each level of concreteness and frequency for each patient is given in Table 8. For both patients there was a significant effect of

TABLE 8. EXPERIMENT 6
ABSTRACT/CONCRETE WORD COMPREHENSION

	Frequency	*Concrete* > 4.47	*Abstract* < 4.47
J.B.R.			
(4.8.80)	A and AA	89	93
(28.6.82)	< 50	65	71
S.B.Y	A and AA	76	91
(6.7.82)	< 50	50	94

Percentage correct for each level of frequency and concreteness.

frequency (J.B.R., $\chi^2 = 20.79$, $P < 0.001$, 1 d.f. and S.B.Y., $\chi^2 = 5.90$, $P < 0.02$, 1 d.f., respectively). There was a highly significant effect of concreteness for S.B.Y. ($\chi^2 = 35.3$, $P < 0.001$, 1 d.f.) with performance on abstract words being much superior to that on concrete. This was not the case for J.B.R. ($\chi^2 = 1.57$, $P > 0.2$). S.B.Y.'s ability to define abstract words was particularly impressive; some examples of his responses are as follows.

Debate	Discussion between people, open discussions between groups.
Malice	To show bad will against somebody.
Deceive	To let people down—give them the wrong ideas and wrong impression.
Caution	To be careful how you do something.

By contrast some examples of his responses to concrete words are as follows.

Ink	Food—you put on top of food you are eating—a liquid.
Frog	An animal—not trained.
Cabbage	Use for eating, material it's usually made from an animal.
Tobacco	One of your foods you eat.

The patient's incorrect responses were rated by three judges according to the same classification adopted by Coughlan and Warrington (1981) as follows.

Omission	Made no attempt at definition.
Vague	Imprecise, residual comprehension indicated (e.g. puppy—'young animal').
Phonological	Responses in which the subject appears to be defining a word phonologically similar to the target word (e.g. *sap*—'kitchen tool device for turning the water on').
Miscellaneous	(e.g. *mutton* 'some sort of rubbish').

TABLE 9 EXPERIMENT 6 ERROR ANALYSIS

	Omission	*Vague*	*Phonological*	*Miscellaneous*
J.B.R.	4	22	27	47
S B.Y.	0	60	11	30

Percentage correct for each type of error.

The percentage for each type of error is given in Table 9. The most interesting aspect of the error analysis is the occurrence of phonological errors, a phenomenon previously reported by Coughlan and Warrington (1981). As in the case of the previous study these errors cannot be attributed to impairment at an early stage of auditory perception as the subject was required to repeat each target word. The main finding of this experiment is, however, the evidence for selective impairment of the knowledge of concrete concepts, which has been recorded twice previously (Warrington, 1975, 1981). S.B.Y. showed this dissociation particularly clearly. It should also be noted that he exhibited this same dissociation in picture-word matching (*see* Case Report).

Experiment 7: Comparison of Multiple Verbal Categories

With verbal stimuli it is feasible to investigate a wide range of categories and so obtain a selection which has not been predetermined by clinical observation. Battig and Montague (1969) have obtained frequency norms for 56 verbal categories; 26 of these were considered appropriate for more detailed investigation of possible category specificity. For the most part exclusion was determined by cultural factors (e.g. US colleges), the lack of sufficient high frequency items (e.g. units of time) or their being proper names (e.g. girls' names).

The test stimuli consisted of 12 items of fairly high category-frequency from each of the 26 categories. J.B.R., tested on two days, attempted to define one item from each category in turn and this procedure was repeated until he had attempted all 312 words. (It was not possible to test S.B.Y. on this experiment.) Since this word pool included categories with items that might be difficult for normal subjects to define precisely (e.g. *metals*, *fish*), a control subject matched for age and occupation with J.B.R. was also tested.

The number correct for each category for J.B.R. and the control subject is given in Table 10.

In order to control for word frequency effects an expected score for each category

TABLE 10. EXPERIMENT 7 BATTIG AND MONTAGUE CATEGORY TEST

	Obtained score	*Expected score*	*Difference score*	*Control score*
1. Clothing	10	8.6	+1.4	12
2. Dwelling	10	9.5	+0.5	11
3. Furniture	10	8.5	+1.5	11
4. Kitchen utensil	10	8.6	+1.4	12
5. Occupation	10	8.6	+1.4	11
6 Body part	10	10.3	−0.3	11
7. Vehicle	10	9.4	+0.6	9
8. Sport	9	8.1	+0.9	9
9. Weather	9	8.8	+0.2	9
10. Crime	8	4.7	+3.3	9
11. Earth formation	8	9.6	−1.6	12
12. Tools	8	8.5	−0.5	11
13. Animals	6	9.5	−3.5	11
14. Science	5	7.1	−2.1	11
15. Insect	3	8.5	−5.5*	10
16. Metal	4	9.6	−5.6*	6
17. Drink	2	6.1	−4.1*	11
18. Cloth	2	8.5	−6.5*	8
19. Musical instrument	2	8.1	−6.1*	12
20. Disease	1	6.7	−5.7*	9
21. Fish	1	7.7	−6.7*	9
22. Precious stone	1	6.1	−5.1*	8
23. Flower	0	5.9	−5.9*	7
24 Fruit	0	7.7	−7.7*	9
25. Tree	0	7.5	−7.5*	8
26. Vegetable	0	6.9	−6.9*	11

J.B.R.'s (5.8.80–8.8.80) and control subject's performance for each category. * Significant difference at $P < 0.05$ between J.B.R.'s obtained and expected scores.

was estimated from J.B.R.'s level of performance in Experiment 6 on five frequency bands of the Brown and Ure pool which span the full concrete/abstract range (AA, A, 10 to 49, 1 to 9, < 1). Each individual word was given an 'expected' score depending upon its frequency band; for instance a word in the frequency band 1 to 9 received a score of 0.58, the probability correct for that band in the previous experiment. The sum of these scores was taken as the expected value for that category (*see* Table 10). For each category the significance of the obtained score and the expected score was computed using an χ^2 test. For the most part J.B.R. either scored at a level commensurate with his overall level on the mixed abstract/concrete pool or at a very low level indeed. Thus on his ten best categories his score averaged more than 80 per cent correct whereas for his ten worst his score averaged less than 10 per cent correct, far worse than the control subject. These categories do include some that the control subject also found somewhat difficult (e.g. *metal*, *tree*). It appeared that the control subject's poor performance on these categories could be attributed to characteristics of this word pool that result in their being somewhat difficult to define other than in terms of the superordinate (e.g. fish) or containing a considerable number of low frequency items (e.g. precious stone). Even allowing for these variations in category difficulty, J.B.R.'s pattern of performance would appear to offer strong evidence for the selective preservation and selective impairment of particular verbal categories.

On this account, the distribution of difference scores would be expected to be bimodal, which it appears to be by inspection. To assess this possibility more formally, Dr I. Nimmo-Smith applied Silverman's (1981) simulation procedure for estimating the number of modes in a distribution. The hypothesis that the obtained scores came from a unimodal distribution could be rejected at $P < 0.005$ significance level.

Turning to the individual categories, the findings of this experiment are in general in accord with the category effects reported in Experiments 2, 3 and 4. There are a number of somewhat anomalous findings that will be discussed below.

Experiment 8: Recognition of Animals, Foods and Inanimate Objects

Clinical assessment of K.B. and I.N.G. indicate fairly marked nominal and expressive difficulties. It was therefore inappropriate to investigate picture and word identification by verbal description. Instead a matching to sample technique was adopted. J.B.R. was also tested. Identification of animals, foods and inanimate objects was tested using a spoken word/picture matching test. The test stimuli consisted of arrays of 5 coloured pictures which were 5 animals, 5 foods or 5 inanimate objects (all taken from the Ladybird books series for young children) and the task was to match the spoken word to one of the 5 items in the array. The patients were tested in blocks of 20 trials; within a block the array remained the same and each of the 5 test stimuli was presented four times in pseudorandom order. The patients were under no pressure to respond quickly; the intertrial interval was approximately 2 s and the interblock interval approximately 2 min. The three stimulus categories were tested in a 3 × 3 Latin Square design, a different set of 5 items being used for each array, giving in all 15 items in each category (*see* Appendix).

The percentage correct for each category for each patient is shown in Table 11. For each patient 3 × 2 contingency tables were drawn up comparing across categories the number of items for which performance was perfect across all four trials with the number where performance was impaired. The contingency tables were then analysed using the Lancaster/Irwin method for partitioning the χ^2 statistic (Everitt, 1977). For all 3 patients there was no significant difference between performance with animals and foods (J.B.R., $\chi^2 = 1.21$, $P > 0.2$, 1 d.f.; K.B. and I.N.G., $\chi^2 = 0$). For all 3 patients performance on inanimate objects was significantly better than the other two categories (J.B.R., $\chi^2 = 13.01$, $P < 0.001$, 1 d.f.; K.B., $\chi^2 = 18.41$, $P < 0.001$, 1 d.f.; I.N.G., $\chi^2 = 5.41$, $P < 0.05$, 1 d.f.). Matching to sample therefore gives completely analogous results to the verbal description procedure.

TABLE 11 EXPERIMENT 8 WORD/PICTURE MATCHING

	Animals	*Foods*	*Inanimate objects*
J.B.R. (25 2.83)	67	60	98
K.B (7.5.81)	45	55	85
I.N.G. (14 6.82)	80	85	97

Percentage correct for each category (Chance = 20 per cent).

DISCUSSION

In this series of experiments we have attempted to document the visual identification and auditory comprehension deficits of 4 patients who had made a partial recovery from herpes simplex encephalitis. These patients were selected for more detailed investigation on the basis of clinical observations that suggested that their knowledge of certain categories of visual objects appeared to be selectively impaired. It had been noted that they all had much greater difficulty in identifying living things than inanimate objects.

The patients differed in one major respect. Two of the patients, J.B.R. and S.B.Y., had fluent spontaneous speech with normal articulation, phrase length and syntax. The other 2 patients, K.B. and I.N.G., however, had marked expressive speech difficulties; only a single experiment using the matching to sample technique was therefore possible. In other respects the pattern of performance of all 4 patients was remarkably similar. Two minor exceptions were noted: (1) the selective preservation of abstract word comprehension in S.B.Y., and (2) the relative preservation of nominal skills in J.B.R. In this discussion we will make the assumption that had it been feasible to test K.B. and I.N.G. using verbal description procedures, their performance would in all critical respects have been similar to that of J.B.R. and S.B.Y.

The major findings of this investigation are as follows.

1. *Category Specificity*

The identification of inanimate objects was remarkably well preserved when compared with the identification of living things and foods. Experiments 2 and 3 established a very striking dissociation between identification of objects and living things. In Experiment 4 it was found that the identification of foods was very impaired as compared with inanimate objects. In Experiments 5 and 8 the same dissociation between inanimate objects and foods and living things was observed. Furthermore our evidence for category specificity is derived from four different methods of assessment, namely, verbal description, naming, mimed responses and picture/word matching. Other aspects of category specificity were explored in Experiments 6 and 7. Comprehension of abstract words was remarkably well preserved in one patient (S.B.Y.) when contrasted with his comprehension of concrete words (Experiment 6). In Experiment 7 a much wider range of categories was probed using the Battig and Montague (1969) stimulus lists. J.B.R.'s knowledge of this range of categories appeared to be distributed bimodally, both when compared with an 'expected' score and with the performance of a matched control subject; knowledge of most categories was either relatively spared or grossly impaired. The significance of these findings is discussed below.

2. *Comparison of Verbal and Visual Modalities*

Although these patients were selected on the basis of visual identification difficulties they were found to have very comparable difficulties in comprehending the spoken word. Experiment 1, which provided a baseline measure of the severity of their visual identification difficulties for comparison with previously reported patients (Warrington, 1975, 1981), also permitted a direct comparison of knowledge within the visual and verbal domains. Their performance was at a very similar level on both tasks. In the three experiments (2, 4 and 5) which explore category specificity in both domains, an identical pattern of selective preservation and impairment was observed.

3. *Response Consistency*

Somewhat different patterns of responses were obtained for presentation of the same stimulus item on separate occasions within a modality and between modalities. In general, with one exception, there was an insignificant degree of consistency for comparison of responses between modalities (4/5). In contrast there was a significant degree of response consistency for all comparisons within a modality (3/3).

4. *Semantic and Phonological Errors*

In Experiments 3 and 4 superordinate (categorical) information was preserved for a high proportion of the items on which subordinate information could not be retrieved. In Experiment 6 that investigated knowledge of the full abstract/concrete range of content words there was also a high incidence of error responses which indicated preservation of superordinate information. In addition a small but significant number of the 'phonological' errors previously observed by Coughlan and Warrington (1981) were recorded.

Our discussion of these findings will concentrate on their relevance for understanding the organization of the semantic systems. But first, we must consider whether any of our findings could be attributed (1) to artefacts of stimulus selection or (2) to other cognitive deficits.

Word frequency is a critical parameter for a wide range of verbal skills in the brain-damaged population (e.g. Howes, 1964; Poeck and Stachowiak, 1975). In our experiments, the test stimuli within each category were as far as possible balanced for word frequency. It is more difficult to balance for visual familiarity, but in Experiment 5 that compared food, animal, and inanimate object pictures, the effects of visual familiarity were partialled out by using the norms of Snodgrass and Vanderwart (1980); category effects were still obtained. Furthermore in a subsidiary experiment on normal subjects we found that the type of food stimuli used were rated the most familiar for a given word frequency (T. Shallice and R. McCarthy, unpublished). Thus one of the categories showing a robust and reliable deficit is also the most familiar.

It is of course possible that past experience might also influence word frequency and visual familiarity for a particular individual. However, the present series consisted of patients of both sexes, with a wide age range (23 to 55 years), who had very varied educational and occupational histories. Furthermore they all suffered from the same viral illness that is known to affect temporal lobe structures bilaterally (Illis and Gostling, 1972) and this was the case for these patients. We would therefore reject any explanation of our central findings in terms of stimulus selection bias or individual variations of cerebral organization.

Secondly, it is necessary to consider the possible confounding effects of associated deficits, in particular amnesia, dysphasia and perceptual impairments. There was evidence of a moderately severe amnesic syndrome in all 4 patients and it might be suggested that their retrograde deficit was so severe that information acquired in early life was not preserved. If, however, loss of knowledge acquired in childhood resulted from the same functional impairment as amnesia then any patient with a severe semantic memory deficit would also have to have a severe amnesic syndrome. This is not the case (*see* Warrington, 1975; Coughlan and Warrington, 1981). Furthermore, the category specificity findings themselves make the retrograde amnesia hypothesis untenable; any suggestion that food names were learned after names of inanimate objects would be absurd. Similarly, the category specificity findings are very difficult to explain in terms of some form of visual processing deficit.

In view of the associated aphasic impairments recorded in all four of these patients it is necessary to consider whether our results were confounded by word-finding difficulties. It is, however, unclear how the impoverished residual expressive vocabularies of our patients would bias their responses against living things and foods and in the case of S.B.Y. in favour of abstract words. In this regard it is worth noting that both J.B.R. and S.B.Y., in addition to being able to recognize colours, had an adequate colour name vocabulary. More critically on the picture/word matching tasks in which no verbal responses were required, equally clear evidence of category specificity was obtained for both the dissociation between the abstract and concrete categories (S.B.Y.) and that between inanimate objects, animals and foods (J.B.R., K.B., I.N.G.). In short, we claim that our findings are not secondary to an amnesic syndrome or to deficits of visual perception or expressive speech. It would appear therefore that the observed comprehension deficits arise within the semantic domain.

Before considering in more detail the significance of category specific impairments we will discuss briefly whether the deficits should be attributed to a degradation of the semantic entries themselves or alternatively to difficulty in the process of accessing the full semantic representation of the concept. It has previously been argued by ourselves (Warrington and Shallice, 1979) that the hallmarks of a degradation deficit are consistency of responding across multiple presentations of the same stimulus, especially the vulnerability of subordinate information and marked frequency effects. These properties were recorded in the present investigation. The relative invariance of identified and unidentified stimuli we interpret as reflecting a static impoverished knowledge base. Our data suggests that there is less correspondence between their knowledge of pictures and words—their visual and auditory vocabularies. Thus a particular concept can be consistently known from its visual representation and consistently *not* known from its verbal representation or of course the converse (the severity of the verbal and visual deficits being much the same). Strictly our arguments apply to the inanimate object category only, as floor and ceiling effects prevented a meaningful consistency analysis (both within and between modalities) for the other categories. Our inference is that two semantic systems—visual and verbal—are implicated and both are impaired in these patients. This conclusion is in accord with the findings reviewed in the Introduction that point to the existence of separate visual and verbal semantic systems.

The major finding of interest in this study is the evidence for category specificity. We have argued that our findings provide compelling evidence for the specific impairment and preservation of semantic information. It then becomes necessary to specify and explain the observed dissociations between preservation of knowledge of inanimate objects and impairment of knowledge of living things and foods. In fact the converse dissociation has already been documented for the auditory modality in a patient (V.E.R.) in whom comprehension of inanimate object names was impaired, food, animal and plant names being preserved (Warrington and McCarthy, 1983). If the categories sampled both in that investigation and the present study are considered, the overall pattern of performance appears to be the same except that the preserved and the impaired categories are reversed. The existence of this double dissociation eliminates any explanation in terms of general task difficulty or the increased vulnerability of particular categories.

In the case of V.E.R. it was argued that the preserved categories were those in which the identification of a particular category member depended upon a differentiation which stressed sensory features. To distinguish between a strawberry and a raspberry depends critically upon fine differences in colour, shape, size and texture. Similarly such information must also be accessed to achieve precise verbal comprehension.

Inanimate objects unlike, say, most animals and plants, have clearly defined functions. The evolutionary development of tool using has led to finer and finer functional differentiations of artefacts for an increasing range of purposes. Individual inanimate objects have specific functions and are designed for activities appropriate to their function. Consider, for instance, chalk, crayon and pencil; they are all used for drawing and writing, but they have subtly different functions. Their crucial defining characteristic is their use with a particular writing surface, for example, blackboard, drawing paper, writing paper. Similarly, jar, jug and vase are identified in terms of their function, namely, to hold a particular type of object, but the sensory features of each can vary considerably. By contrast, functional attributes contribute minimally to the identification of living things (e.g. lion, tiger and leopard), whereas sensory attributes provide the definitive characteristics (e.g. plain, striped, or spotted). We would suggest that identification of an inanimate object crucially depends on determination of its functional significance, but that this is irrelevant for identification of living things. We would therefore speculate that a semantic system based on functional specifications might have evolved for the identification of inanimate objects. The other major categories we have considered might well have some representation in such a system, but this, we assume, would be inadequate for precise identification. To achieve precise identification for foods and living things, other semantic systems based on sensory features would be required (*see* Warrington and McCarthy, 1983). Such semantic systems would presumably have different patterns of associative links with other cognitive systems such as those underlying action and intention and associative links with other sensory modalities.

This distinction between functional significance and sensory features is clearly applicable to the major categorical dissociation we have observed, namely, those between inanimate objects on the one hand and living things and foods on the other. How does this distinction relate to our findings on the wider range of categories sampled in Experiment 7? The observation of a bimodal distribution of performance between those categories that are relatively spared and those that are grossly impaired supports the concept of category specific preservation and impairment. Although the findings for many of the individual categories selectively preserved or impaired are in good accord with our major distinction, this formulation may well be incomplete. For instance the distinction is hardly applicable to categories such as weather and land formation (both preserved categories). We note that impaired categories include cloths and precious stones, which are inanimate objects. We would argue, however, that these categories have only a 'generic' function and that such stimuli might be more easily differentiated by their sensory features. A more abstract category—diseases—can perhaps also be understood in these terms.

The major anomalies to emerge are the findings that J.B.R. obtained a very poor score indeed on the musical instrument category and a relatively good score on body parts. Whether these results reflect the confounding effects of word frequency or whether there is a more fine grain categorical organization of semantic systems than has hitherto been supposed needs to be clarified by further studies. Nevertheless evidence for category specificity, *per se*, would appear to be robust. The dissociations are striking and generalize over a wide range of stimuli.

Further support for a more general level of category specificity within the semantic systems is provided by the findings on the comprehension of abstract words. The relative preservation of the comprehension of abstract concepts compared with concrete concepts has been previously reported (Warrington, 1975). S.B.Y. (Experiment 6) provides a very clear second instance of this unexpected syndrome. His comprehension of low frequency abstract words was nearly perfect, far superior to his comprehension of concrete words of equivalent frequency. (For further discussion of the significance of category specificity, *see* Warrington and McCarthy, 1983.)

Neurological Considerations

All 4 patients described here were diagnosed as cases of herpes simplex encephalitis. In each, there was evidence of bilateral brain disease affecting in particular the temporal lobe structures. The severe global amnesic sydrome present in all 4 patients has frequently been described in herpes simplex encephalitis and is well recognized to be associated with bilateral temporal lobe disease. The neuropsychological syndrome we have described in this investigation—a specific impairment of visual and verbal identification—would generally be accepted as lateralized to the left hemisphere, the temporal and ventral occipital regions being considered critical structures (Hécaen and Albert, 1978; Coughlan and Warrington, 1978). The lesions in our patients were widespread but included these regions.

Of particular neurological interest is that features of the Klüver-Bucy syndrome are a not infrequent feature in the acute phase of herpes simplex encephalitis (*see* Hierons *et al.*, 1978). Greenwood *et al.* (1983) have discussed this aspect of the illness in more detail and conclude that a more frequently observed symptom is bizarre eating and drinking behaviour. Three of our 4 patients were indeed observed to eat and drink indiscriminately in the acute phase. As we have documented a severe difficulty in identifying foods and comprehending food names in these patients the question arises as to whether their agnosia is causally related to the Klüver-Bucy syndrome or is an associated deficit.

We have described a new constellation of deficits in which, broadly speaking, visual identification and verbal comprehension of living things and foods appear to be selectively impaired and inanimate objects selectively preserved. Further investigation will establish whether or not this is a commonly occurring syndrome in patients with herpes simplex encephalitis.

ACKNOWLEDGEMENTS

We wish to thank Dr L. J. Findley, Professor J. Marshall, the late Dr R. T. C. Pratt and Dr Michael Trimble for permission to investigate patients under their care and to report our findings. T.S. is a member of the Medical Research Council Applied Psychology Unit, and we wish to acknowledge the Council's support. We are grateful to J. Willison, C. Maciejewski and Dr K. Lewis who rated our subjects' responses. We particularly wish to thank Dr Ian Nimmo-Smith for his invaluable statistical advice and assistance.

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(*Received August 18, 1983. Revised January 3, 1984*)

(*See overleaf for Appendix*)

APPENDIX

Stimuli used in Experiment 2

Animate stimuli

	Freq		*Freq*		*Freq*
Peacock	33	Hedgehog	11	Panda	9
Deer	316	Lobster	29	Palm	119
Rose	461	Daffodil	6	Buttercup	4
Chestnut	24	Frog	171	Crab	62
Duck	216	Ladybird	2	Acorn	10
Camel	72	Holly	24	Wasp	32
Giraffe	40	Owl	137	Sheep	464
Kangaroo	43	Bear	557	Rabbit	209
Crocodile	61	Tulip	20	Ostrich	33
Parrot	94	Mouse	207	Beetle	41
Butterfly	77	Foxglove	0	Rhino	14
Tortoise	17	Eel	24	Shark	92
Fox	163	Poppy	15	Seaweed	41
Donkey	156	Toadstool	4	Squirrel	88
Crocus	0	Snail	47	Swan	29
Flamingo	7	Lizard	54	Spider	229

Inanimate stimuli

	Freq		*Freq*		*Freq*
Car	1752	Lighthouse	51	Scales	185
Submarine	122	Tent	208	Spade	7
Spanner	0	Decanter	0	Mittens	3
Thermometer	154	Kettle	88	Briefcase	3
Torch	28	Stool	58	Tankard	2
Violin	106	Towel	48	Wallet	13
Vice	14	Mincer	0	Axe	27
Piano	418	Toaster	16	Typewriter	43
Ladder	127	Scissors	72	Calculator	4
Saw	2900	Barometer	42	Binoculars	20
Drill	136	Canoe	164	Hammer	155
Tennis racket	24	Trumpet	77	Compass	210
Wheelbarrow	21	Windmill	33	Tricycle	10
Dustbin	0	Slippers	38	Headphones	3
Hoover	22	Guitar	101	Pram	0
Mop	16	Umbrella	51	Drums	128

The word frequencies were taken from the Carroll *et al* (1971) count Where appropriate the frequency of the American equivalent is given

Stimuli used in Experiment 4

Food	*Freq*	*Inanimate*	*Freq*
Grapefruit	18	Rollerskates	2
Mixed nuts	143	Paint box	3
Cabbage	139	Swing	89
Pineapple	39	Balloon	233
Cake	244	Mirror	209
Cucumber	6	Camera	166
Beer	24	Crayon	83
Bread	515	Bicycle	182
Eggs	785	Cotton reel	12
Chocolate	143	Umbrella	51
Meat	617	Wheelbarrow	21
Tomatoes	49	Clothes peg	4
Orange	221	Pram	3
Biscuits	45	Button	130
Cheese	236	Mitten	3
Pear	32	Sandal	5
Ice cream	33	Belt	174
Soup	184	Double bass	2
Milk	849	Skipping rope	1
Sprouts	8	Trumpet	77
Lemon	44	Tankard	2
Strawberry	26	Basin (sink)	149
Baked beans	199	Radiator	25
Lolly	8	Shears	30
Onion	42	Electric fire	—
Mushroom	43	Scales	185
Chips	42	Jigsaw	8
Peas	70	Slide	182
Jelly	87	Drums	128
Apples	284	Tie	234

Brain (1984), **107**, 855–870

NEURO-OPHTHALMOLOGY OF SPHENOID SINUS CARCINOMA

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SUMMARY

Three cases of sphenoid sinus carcinoma observed personally and 39 identified in the English language publications are reviewed. Sphenoid carcinoma constitutes only 0.3 per cent of sinus cancer. Its symptoms and signs are nonspecific until the sinus wall is penetrated. Once breached, specific neuro-ophthalmological symptoms and signs ensue, resulting from involvement of anatomically contiguous structures. These are characterized most commonly by the sphenocavernous syndrome and less frequently by isolated sixth nerve palsies and visual loss. Identified best by plain radiography, polytomography and computerized tomography, diagnosis of sphenoid carcinoma requires direct biopsy. Treatment, principally with radiotherapy supplemented by chemotherapy, has been disappointing with most patients dead by three years. The authors believe that in rapidly evolving neuro-ophthalmological syndromes of basal origin, accompanied by intractable headache, sphenoid sinus cancer must be considered.

INTRODUCTION

The sphenoid sinus has been called the neglected sinus; its existence was not recognized until the description by Vesalius in 1515 and it was not known to harbour disease until Rouge discovered sphenoid sinusitis at an autopsy in 1871 (Cavanaugh, 1935). Disease of the sphenoid sinus remains uncommon, or at least infrequently diagnosed, but when it occurs it is apt to produce neuro-ophthalmological complications. Carcinoma of the sphenoid sinus is a case in point. Initially described in 1891, it is rare, comprising only about 0.3 per cent of all malignancies of the paranasal sinuses (Spencer and Gall, 1923; DeJean, 1927; Larsson and Maartensson, 1954; Hara, 1955; Judd, 1960; McCarthy and Lawrence, 1975; Jackson *et al.*, 1977). However, it may present with dramatic neuro-ophthalmological symptoms and signs. The neuro-ophthalmological features of this tumour will be illustrated by describing 3 of our cases and reviewing 39 others culled from English language publications (Table 1).

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TABLE 1 CLINICAL SUMMARY OF COLLECTED CASES OF SPHENOID SINUS CANCER

Source	*Case no*	*Age*	*Sex*	*Presenting symptoms*	*Neuro-ophthalmological*		*Neurological signs and symptoms*	*Nonneurological signs and symptoms*	*Histopathology*	*Treatment and course*
					Syndrome	*Findings*				
Alexander (1963)	1	61	M	Headache	Isolated VI nerve palsy	R VI nerve palsy	None reported	None reported	Plasmacytoma	Surgery followed by irradiation, alive 6½ yrs later
	2	58	M	Headache, lymph node metastases	Isolated VI nerve palsy	L VI nerve palsy	None reported	Extensive bony metastases	Undifferentiated carcinoma	Died after 21 m
Banna (1977)	3	58	F	Headache, visual loss R, facial paraesthesiae	Spheno-cavernous syndrome	R II, III, IV, V VI nerve palsy, R proptosis	None reported	None reported	Squamous cell carcinoma	Irradiated, survival unknown
Bennett (1964)	4	60	M	Diplopia	Spheno-cavernous syndrome	L III, IV, V, VI nerve palsy	Headache	Epistaxis	Transitional cell carcinoma	Irradiated, died at 20 m later
	5	34	M	Diplopia	Isolated VI nerve palsy	R VI nerve palsy	None reported	None reported	Plasmacytoma	Chemotherapy, died at 10 m later
	6	65	M	Headache, diplopia	Isolated VI nerve palsy	R VI nerve palsy	None reported	R otitis media	Transitional cell carcinoma	Irradiated, died 30 m later
	7	58	M	Diplopia, epistaxis, hearing loss	Isolated VI nerve palsy	L VI nerve palsy	Hemiplegia and coma (late in course)	None reported	Transitional cell carcinoma	Irradiated, died 1 w later
	8	19	F	Lymph node metastases	Isolated VI nerve palsy	R V, VI nerve palsy	Headache	Otitis media	Transitional cell carcinoma	Irradiation with chemotherapy, died after 27 m
	9	56	M	Diplopia	Not reported	Not reported	Increased intracranial pressure, hemiparesis and coma	None reported	Lymphoma	Died after 12 m
Davison and Kahr (1931)	10	43	M	Headache	Sphenocavernous syndrome	R III, VI and L V, VI nerve palsy	Bilateral anosmia, R IX, X, XII nerve palsy, bilat Babinski responses	None reported	Squamous cell carcinoma	Died after 7 m
	11	55	M	Diplopia	Sphenocavernous syndrome	R III, V, VI and L III, VI nerve palsy	Headache, L VII, VIII, IX, X, XI, XII nerve palsy	Cervical lymph node metastases	Squamous cell carcinoma	Irradiation, died 8 m later
Dombrowski (1895)	12	50	F	Headache, visual loss	Optic nerve compression	Bilat optic nerve involvement	None reported	None reported	Papillary carcinoma	Surgery, died 2–3 yrs later
Gay (1962)	13	30	M	Ptosis, diplopia, facial sensory loss	Sphenocavernous syndrome	R III, V nerve palsy	Headache	None reported	Epidermoid carcinoma	Irradiation, lost to follow-up
Harbison (1984) Present series	14	55	M	Visual loss	Optic nerve and chiasmal compression	Bilat optic nerve and chiasm compression	L VII nerve palsy	None reported	Squamous cell carcinoma	Irradiation and chemotherapy, died 7 m later
	15	47	M	Headache	Sphenocavernous syndrome	R II, III, IV, V, VI nerve palsy, R proptosis	None reported	None reported	Undifferentiated carcinoma	Surgery and irradiation, alive at 1 yr
	16	54	M	Visual obscurations	Increased intracranial pressure	Papilloedema	None reported	None reported	Mucoepidermoid carcinoma	Lost to follow-up
Hardie and Ahronheim (1943)	17	50	F	Dental, ear and mastoid pain	Isolated VI nerve palsy	L VI nerve palsy ?L optic nerve,? ?papilloedema	Headache	Sinus infection	Squamous cell carcinoma	Irradiation, died 20 m later

Hirsch (1958)	18	64	M	Visual loss	Sphenocavernous syndrome	'Bilat ophthalmoplegia and blurred vision'	None reported	None reported	Transitional cell carcinoma	Irradiation, lost to follow-up
	19	32	M	Headache	Sphenocavernous syndrome	R III, IV, VI and L III, IV, VI nerve palsy	'Entire brainstem involved'	None reported	Adenocarcinoma	Irradiation, died 7 m later
	20	3	—	Visual loss	Optic nerve compression	Bilateral optic nerve involvement	'Drowsiness'	None reported	Undifferentiated sarcoma	Irradiation, died 3½ yrs later
Levine (1978)	21	—	—	Distant metastases	None reported	None reported	None reported	None reported	Adenocarcinoma	Not reported
	22	—	—	Not reported	None reported	None reported	Headache, 'several cranial nerves'	None reported	Lymphoepitheloma	Not reported
	23			Not reported	None reported	None reported	Headache	None reported	Chondrosarcoma	Not reported
McCarthy and Lawrence (1975)	24	60	M	Headache, diplopia	Sphenocavernous syndrome	R III, VI and L III, IV, V VI nerve palsy	Headache	None reported	Undifferentiated squamous carcinoma?	Irradiation, survival not noted
Mass Gen Hosp Case records (CPC) (1948)	25	65	F	Facial pain, ptosis	Isolated III nerve palsy	R III nerve palsy	Headache	Bloody nasal discharge	Transitional cell carcinoma	Irradiation, lost to follow-up
Meyer (1962)	26	63	F	Facial paraesthesiae	Sphenocavernous syndrome	R III, IV, VI and L V nerve palsy	Headache, R III, XI-XII nerve palsy, gait disturbance	Lymph node metastases	Carcinoma adenoides cysticum	Irradiation, died at 26 m later
Tassman (1947)	27	58	F	Headache	Sphenocavernous syndrome	R optic nerve R III, IV, V, VI nerve palsy	Headache	Epistaxis	Carcinoma	Not reported
Tolan (1939)	28	66	F	Headache	Sphenocavernous syndrome	L optic nerve, L proptosis	Headache	None reported	Transitional cell carcinoma	Irradiation, living 18 m later
Van Wart (1973)	29	46	M	Headache	Isolated VI nerve palsy	Bilateral VI nerve palsy	Headache, R IX to XII	None reported	Squamous cell carcinoma	Irradiation, died at 4 m
	30	66	M	Headache, facial paraesthesiae	Sphenocavernous syndrome	L III, V, VI, L proptosis	Personality change, headache, dysphagia, confusion	None reported	Squamous cell carcinoma	Irradiation, died 6 m later
	31	52	M	Headache	Sphenocavernous syndrome	L III, VI, L proptosis	Headache	None reported	Squamous cell carcinoma	Irradiation, died 14 m later
	32	52	M	Headache	Isolated VI nerve palsy	R VI	Headache	None reported	Squamous cell carcinoma	Irradiation, died 24 m later
	33	78	M	Not reported	Not reported	Not reported	Not reported	Not reported	Squamous cell carcinoma	Irradiation, living 6 yrs later
	34	54	M	Headache, diplopia	Isolated VI nerve palsy	R VI	Headache	None reported	Plasmacytoma	Irradiation, living 2 yrs later
White (1927)	35	45	M	Visual loss	Sphenocavernous syndrome	L proptosis L optic nerve and L III	Headache, terminal streptococcal meningitis	None reported	Carcinoma	No treatment, dead in 1 week
	36	35	M	Visual loss	Optic nerve compression	Bilateral optic nerve involvement	Headache, streptococcal meningitis	None reported	Carcinoma	Radium, died 3 m later
Wylie *et al* (1973)	37	—	M	Individual patients not identified in this series Author's comment '3 patients had blurred or double vision on presentation'	Author's comment on the series '5 to 6 had visual alterations All 6 had physical evidence of disease with proptosis and cranial nerve involvement'		4 patients had headache	None reported in series	Adenocarcinoma	All 6 were apparently treated with irradiation, survival ranged from 7 to 33 m
	38	—	M							
	39	—	M						Squamous cell carcinoma (3)	
	40	—	F							
	41	—	F							
	42	—	M						Lymphoepithelioma (2)	

CASE REPORTS

Case 1

A previously healthy 55-year-old man noted dim vision in his left eye. Within three weeks both eyes were involved, with vision reduced to 20/200 in the right eye and light perception in the left. Tangent screen examination showed a temporal hemianopic defect in the visual field of the right eye. On admission to hospital several days later vision in the right eye was reduced to finger counting at 2 feet. Plain skull radiographs and polytomography showed a soft tissue density filling the sphenoid sinus and eroding its floor inferiorly and anteriorly. No evidence of lateral or superior extension could be documented by arteriography or pneumoencephalography. The CSF contained no cells and had a protein content of 0.28 g/l. Cytological studies on the CSF were unremarkable. Transnasal biopsy of the sphenoid showed that the mass was a squamous cell carcinoma.

He received a six week course of radiotherapy and within weeks of completion, vision in the right eye recovered to 20/20. However, despite additional methotrexate chemotherapy visual acuity in this eye again began to decline so that four months after discharge acuity was only 20/50. Both optic discs were now pale. At this time he developed a left lower motor neuron facial paralysis. Thereafter his condition deteriorated rapidly with pulmonary and hepatic metastases and he died of pneumonia seven months after the onset of symptoms.

Case 2

A 47-year-old man was awakened from sleep by a severe headache. On arrival at the hospital his blood pressure was 280/130 and temperature was 39.4° C. Visual acuity was 20/50 on the right and 20/20 on the left. He had 3 mm of proptosis, and complete ptosis and ophthalmoplegia on the right. There was anaesthesia in the distribution of the first division of the right trigeminal nerve. Nasopharyngeal examination was negative and plain skull radiographs were normal. His CSF was unremarkable. The differential diagnosis included septic cavernous sinus thrombosis, infraclinoid carotid aneurysm, pituitary apoplexy and pituitary abscess.

Over the ensuing few days vision in the right eye declined to 20/100 and the proptosis increased. Repeat lumbar puncture six days after admission showed 572 leucocytes, 90 per cent of which were polymorphonuclear. Orbital venography demonstrated a normal cavernous sinus but polytomography of the sella turcica and sphenoid sinus showed erosion of the floor of the sella by a mass in the sphenoid sinus. Transnasal exploration of the sphenoid showed a firm, yellowish-red neoplasm eroding the superior and lateral walls. The histopathological diagnosis was undifferentiated carcinoma. The remaining tumour was irradiated with 60 grays over eight weeks. Two months after completion of therapy, visual acuity was 20/20 in both eyes. Proptosis had disappeared and motility had improved. One year later the patient had moderate ptosis on the right and a large sluggish right pupil.

Case 3

A 54-year-old man suffered four brief syncopal episodes followed on one occasion by 2 h of bilaterally blurred vision. Examination was negative and the syncopal episodes ceased with propanthelene therapy. Six months later he began to experience brief visual obscurations. General medical and neurological examination was negative except for bilateral papilloedema. Plain skull radiographs, EEG, radionucleide brain scan, pneumoencephalogram and carotid arteriography were unremarkable. Lumbar puncture showed an opening pressure of 460 mm CSF with normal chemistry and no cells. Polytomography of the sphenoid sinus revealed a soft tissue density in the floor of the left sphenoid sinus extending into the nasopharynx. Endocrine evaluation was normal. A two week trial of dexamethasone and glycerol did not alter the CSF pressure. Transpalatal sphenoidotomy revealed a mucoepidermoid carcinoma.

DISCUSSION

Anatomical Considerations

The sphenoid sinus is a paired structure that develops in the third fetal month as an evagination of the nasal mucosa into the posterior portion of the cartilagenous nasal capsule. Ossification begins in the fifth fetal month and is well advanced at birth. Pneumatization is limited in the early years of life and generally not complete until the fourteenth or fifteenth year (Van Alyea, 1941). The size and shape of the sinus cavity is highly variable but it generally has a rectangular form with six surfaces, and a large number of important structures have been identified in contact with these surfaces (Levine, 1978).

The pituitary fossa forms the roof of the posterior portion of the sphenoid sinus. Anteriorly, a variety of structures are closely associated, among them, the ethmoid sinus, the nasal cavity and often the posterior and medial aspects of the orbit. Related inferiorly are the nasopharynx and eustachian tube. Posteriorly the wall of the sinus is formed by the clivus, bringing the sphenoid into proximity with the brain stem and lower cranial nerves. Posterolaterally the sphenoid sinus abuts the petrous bone and the fifth to eighth cranial nerves inclusive. The sinus wall is formed anterolaterally by the superior orbital fissure and posterolaterally by the cavernous sinus. Intimately associated anterolaterally in the superior aspects of the bony sinus wall are the optic nerves. The actual proximity of these structures to the sinus is dependent upon the extent of pneumatization, since pneumatization ultimately determines the thickness of the bony wall. Sometimes a paper-thin wall separates the sinus from adjacent structures and, rarely, portions of the wall are absent (Sluder, 1927; Proetz, 1948). In the case of the optic nerve, Young (1924) has suggested that bony defects are common between the sinus and the optic canal. He dissected 30 fresh unselected specimens at post-mortem and found bony hiatuses in 4 cases (13 per cent), with one specimen demonstrating extensive bony absence. The process of pneumatization is not restricted to the sphenoid bone and may extend into adjacent bones including the greater and lesser wing of the sphenoid, the base of the pterygoid process, the anterior and posterior clinoids and the basilar portion of the occipital bone (Sluder, 1927; Van Alyea, 1941). Instances in which a neighbouring structure (such as the optic nerve) is entirely surrounded by pneumatized sphenoid sinus have been recorded (Onodi, 1910; Mellinger, 1937). Thus the anatomical situation is such that a carcinoma limited to the body of the sphenoid may produce only vague and ill-defined symptoms, but when it extends beyond the confines of the sinus, specific signs and symptoms develop based upon the proximity and vulnerability of surrounding structures.

Malignancy of the Sphenoid Sinus

Malignancies of the paranasal sinuses comprise between 0.2 and 2 per cent of all human cancers (Bennett, 1964). Maxillary and ethmoid carcinomas are the most common, frontal and sphenoid carcinoma are held to be quite rare. Statistics on the frequency of primary carcinoma of the sphenoid sinus are available from several institutions (Cranmer, 1953; Larsson and Maartensson, 1954; Hara, 1955; Lewis and Castro, 1972; Adams *et al.*, 1974; Jackson *et al.*, 1977). A review of series from six large centres showed that only 4 of 1271 cases of paranasal sinus malignancies originated in the sphenoid sinus (Table 2). Thus, sphenoid sinus carcinoma appears to constitute only 0.3 per cent of all paranasal sinus malignancies.

TABLE 2 INCIDENCE OF SPHENOID ORIGIN OF PRIMARY PARANASAL SINUS MALIGNANCY

Author	*Time period of series*	*Institution*	*Total paranasal sinus malignancies*	*Sphenoid sinus origin*
Adams *et al.* (1974)	1959–1971	University of Minnesota Hospitals	75	0
Cranmer (1953)	1932–1948	University of Michigan Hospitals	91	0
Hara (1955)	1935–1954	Los Angeles County Hospital	92	0
Jackson *et al.* (1977)	1957–1974	University of Virginia Hospital	96	1
Larsson and Maartensson (1954)	1940–1950	Karolinska Sjukhuset	379	0
Lewis and Castro (1972)	30 yrs	Memorial Hospital, New York	538	3

Because the early symptoms may be vague and nonlocalizing, sphenoid sinus carcinomas may be far advanced before they are diagnosed. In some instances this makes it difficult to determine where the tumour originated (Watson, 1942). Usually, however, information about the distribution of the tumour and its clinical course can be combined to trace the process to its origin. The reason for the low incidence of malignancy in the sphenoid sinus is not known. It may be related to the paucity of glandular elements in its mucosa or to its location, where, outside the mainstream of the respiratory tract, it is protected from inhaled carcinogens (Gleitsmann, 1905; Dixon, 1937; Wyllie *et al.*, 1973; Robin and Shortridge, 1979).

There were twice as many men as women in our collected series of cases, a distribution similar to that for all paranasal sinus malignancies. The age range was wide—from 3 to 78 years. The sixth decade was the most common time of presentation, again in keeping with the onset of all paranasal sinus malignancies (*see* figure). The most frequent histological type was squamous cell carcinoma (15 cases), followed by transitional cell carcinoma (7 cases). Many additional cell types have been reported and are listed in Table 3.

TABLE 3. CELL TYPE OF PRIMARY SPHENOID MALIGNANCY

Cell Type	*Incidence*
Squamous cell carcinoma	14
Transitional cell carcinoma	7
Adenocarcinoma	4
'Carcinoma', not further defined	3
Plasmacytoma	3
Lymphoepithelioma	3
Undifferentiated carcinoma	2
Chondrosarcoma	1
Lymphoma	1
Undifferentiated sarcoma	1
Papillary carcinoma	1
Mucoepidermoid carcinoma	1
Epidermoid carcinoma	1

Presentation of Sphenoid Sinus Malignancy

The presenting symptoms of the lesion were documented in 36 of the 42 cases reviewed: 51 complaints were recorded, indicating that some patients had multiple symptoms at presentation. There were only 11 independent symptoms among the 51 complaints (Table 4). Of these 11, 5 can be considered neuro-ophthalmological in character: visual loss, diplopia, ptosis, visual obscurations, and facial pain or paraesthesiae. The remaining presenting complaints were for the most part neurological. The single most frequent was headache which occurred in 16 patients. In half of them it was the *only* presenting symptom.

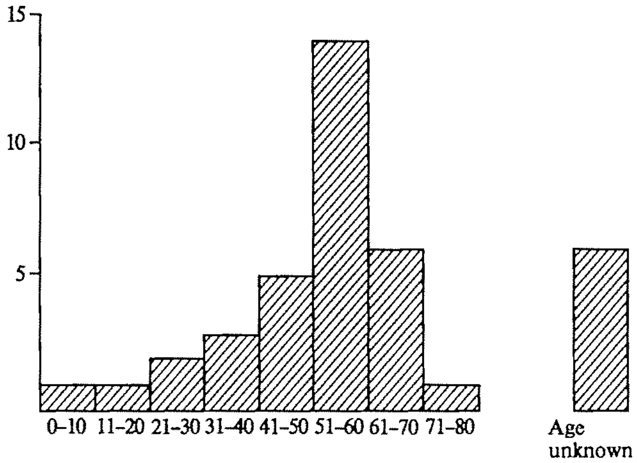

FIG. Profile of age of presentation in sphenoid cancer.

TABLE 4 PRESENTING SYMPTOMS IN 35 PATIENTS WITH PRIMARY MALIGNANCY OF THE SPHENOID SINUS*

Symptoms	*No. of times reported*
Headache	16
Diplopia	13
Visual loss	7
Facial pain/or paraesthesiae	5
Distant metastases	3
Ptosis	2
Epistaxis	1
Hearing loss	1
Altered consciousness	1
Visual obscurations	1
Dental, ear and mastoid pain	1

* Unknown in 6 cases.

The Neuro-ophthalmological Involvement

Incidence of neuro-ophthalmological symptoms and signs. Only 29 of the 42 cases reviewed were described in sufficient detail to allow critical analysis of the signs and symptoms, and all 29 had distinct neuro-ophthalmological features. Of the remaining 13 cases in which the clinical details seemed insufficient, 10 had strong evidence of neuro-ophthalmological involvement. We therefore conclude that nearly all patients with sphenoid sinus malignancy have neuro-ophthalmological symptoms and signs at some time in their course.

When these clinical symptoms and signs are analysed, three neuro-ophthalmological presentations stand out. These are the sphenocavernous syndrome, isolated sixth nerve paralyses, and visual loss. Of these the sphenocavernous syndrome is the most prevalent and was evident in 20 of the cases reviewed. We use the term sphenocavernous syndrome as an inclusive generic designation for the orbital apex syndrome, superior orbital fissure syndrome and cavernous sinus syndrome. It consists of involvement of the third, fourth and sixth cranial nerves as well as the first and second divisions of the fifth cranial nerve. Involvement of the optic nerve and oculosympathetic fibres is not infrequent. Pain may be prominent, and proptosis (variably associated with signs of orbital congestion) is often present. Isolated abducens paresis, not infrequently accompanied by trigeminal nerve signs and symptoms, was next in frequency (9 cases). Involvement of the optic nerve or chiasma was the predominant picture in 5 cases. Less frequent neuro-ophthalmological signs are listed in Table 5.

Anatomicoclinical correlation. The neuro-ophthalmological syndromes consistently produced by sphenoid sinus malignancy are best understood in the context of the anatomy. The proximity of the sphenoid sinus to neighbouring structures is largely a result of the degree of pneumatization of the sinus (Sluder, 1927; Van Alyea, 1941). Pneumatization, which determines the size, configuration and extent of the sphenoid air cells, moulds the thin bony wall of the sphenoid about resisting and immovable surrounding structures. It also determines the thickness of the sinus wall and the degree to which sinus air cells extend into surrounding bone. These factors must, to a very great extent, influence the clinical presentation and course of sphenoid cancer (Mosher, 1903; Sluder, 1913, 1927; Houser, 1932; Van Alyea, 1941; Hardie and Ahronheim, 1943; Bennett, 1964).

Of the structures that adjoin the sphenoid sinus it is clear that the second to sixth cranial nerves are primarily implicated in the symptoms at presentation. Involvement of the remaining structures would not be expected to produce early signs. For example, involvement of the pituitary gland and internal carotid artery would be expected only late in the course of the illness, if at all. Clinical information gleaned from our review confirmed this premise. No case of hypopituitarism and only two instances of hemiparesis were documented.

The sites at which the cranial nerves are involved can be inferred from the anatomy. Whether these sites indicate the origin of the malignant process or simply indicate the path of least resistance, is unclear. However, the fact that the tumour generally fills the sinus by the time it extends beyond its anatomical limits favours the latter explanation.

The optic nerve is presumably involved in the superior and anterior portion of the sinus where the medial aspect of the optic canal forms part of the sinus wall. The wall may be very thin and the entire canal surrounded by sphenoid air cells (Onodi, 1910; Mellinger, 1937). Not infrequently defects are present in the bony wall, increasing optic nerve vulnerability (Young, 1924). The ease of involvement of the optic nerve can be easily understood. Involvement of the third, fourth, first division of the fifth and sixth cranial nerves seems to occur at the level of the superior orbital fissure (Van Alyea, 1941). This important conduit for cranial nerves entering and leaving

TABLE 5. NEURO-OPHTHALMOLOGICAL SYNDROMES OBSERVED IN 42 CASES OF PRIMARY SPHENOID SINUS CANCER

Syndrome		*No. of cases*
Sphenocavernous syndrome		21
with proptosis	12	
without proptosis	9	
Isolated VI nerve palsy		10
Unknown*		5
Optic nerve/or chiasmal involvement		4
Papilloedema		2
Isolated III nerve palsy		1

* In 5 cases, although symptoms of neuro-ophthalmological quality were reported, they were insufficient for identification of the syndrome (e.g. diplopia)

the orbit is adjacent to the anterior and lateral walls of the sphenoid. The nerves often bulge into the sinus wall and, when the sinus air cells extend into the sphenoid wing, the sinus may completely surround the nerve. It is likely that the isolated abducens nerve paresis occurs from lesions at the level of Dorello's canal (*see* Sears, 1926). Here the sphenoid forms the medial wall of the canal. Studies by Houser (1932) have demonstrated that this wall is 2 mm thick or less in 10 per cent of patients. In 31 per cent it is 4 mm or less.

The sphenocavernous syndrome. Twelve of the 20 cases of sphenocavernous syndrome had proptosis. This would suggest extension to the orbital apex or the cavernous sinus. There is a clear tendency for sphenoidal cancer to erode bone aggressively and it may be that the extension through the middle cranial fossa and superior orbital fissure is responsible for the proptosis. There also may be extension from the anterior sphenoid recess directly into the posterior orbit (Godtfredsen, 1947). Most authors have concluded that invasion of the cavernous sinus is rarely the mechanism of the sphenocavernous syndrome in this disease (Van Alyea, 1941).

Visual loss. Ten of the 42 cases of sphenoid cancer had visual loss during the course of their disease. In 4 the loss of vision was an isolated complaint. In those cases with a more extensive clinical presentation, the additional signs most frequently noted were of the sphenocavernous syndrome. This association which was reported in 5 cases is not surprising in view of the proximity of the optic canal, the orbital apex and superior orbital fissure. Visual impairment was unilateral in 6 cases and bilateral in 4. Chiasmal extension was discernible in only one instance. The frequent incidence of visual loss both with and without an associated sphenocavernous syndrome again suggests that sphenoid carcinomas tend to arise in or extend preferentially through the anterior portion of the sinus.

Cranial nerve damage. Cranial nerve involvement in virtually any combination proved to be both the single most frequent neurological and neuro-ophthalmological sign, occurring in 38 of the 42 patients. Multiple nerve involvement was present in 26 instances, 20 constituting the sphenocavernous syndrome. Isolated cranial neuropathies were noted in 12 cases, the abducens accounting for 8, the optic in 3 and the oculomotor on a single occasion. Cranial nerves were compromised unilaterally in 19 cases (11 right and 8 left), bilaterally in 11. Laterality was not stated in 8 instances.

The frequency and extent of cranial nerve involvement suggests that sinus wall erosion occurs at several independent points either simultaneously or in rapid sequence. An anterolateral preference is evident from the clinical prominence of the sphenocavernous syndrome.

Other Neurological Involvement

The most common neurological symptom was headache. It was the presenting complaint in 16 cases and occurred sometime in the course in 15 others. The headache was commonly described as severe, deep-seated and boring. No consistent localization was observed. However, in 7 of the 14 patients with prominent orbitofrontal headache, the clinical course was dominated by the sphenocavernous syndrome. Of the 7 patients with prominent occipital localization of the headache, the clinical course was characterized by petrous apex extension with involvement of the fifth and sixth cranial nerves in 4 of them. This suggests that the headache may reflect the origin or direction of extension of the malignancy. Headache often proved to be the single most incapacitating symptom during the illness, although it tended to respond well to palliative irradiation therapy.

Neurological signs not of a neuro-ophthalmological nature were documented in 14 patients and most commonly resulted from involvement of the lower cranial nerves. The ninth, tenth, eleventh and twelfth cranial nerves were involved in 6 cases (generally unilaterally and in combination). There were 3 patients with eighth nerve and 4 patients with seventh nerve involvement. The lower cranial nerve lesions presumably result from extension of the tumour into the petrous and occipital bones. Six of the patients with involvement of lower cranial nerves also had anterior signs (5 with the sphenocavernous syndrome and 1 with visual impairment). This indicates that extension of the sphenoid cancer can be multicentric.

Increased intracranial pressure was documented in only 3 cases, 2 with papilloedema. This was the presentation in our third patient whose obscurations of vision secondary to papilloedema were the presenting complaint. The mechanism of the pressure elevation was obscure in all 3 cases, but it would seem unlikely that it was simply the consequence of a mass effect. It is possible that there was leptomeningeal spread of tumour with a defect in CSF absorption but this is purely speculation and is unsupported by the normal CSF cytology in our case. Infrequently noted neurological signs and symptoms are listed in Table 6. Most are satisfactorily explained by direct tumour invasion of the skull base and subarachnoid space.

Nonneurological complaints. It was surprising how infrequent nonneurological symptoms and signs were in the series. All the nonneurological signs involved the ear, nose and throat. Four patients had epistaxis (the presenting complaint in one case). There was otitis media in 2 instances, both associated with ipsilateral lower motor neuron seventh nerve paralysis. The low incidence of ear, nose and throat symptoms may indicate that penetration of the nasal cavities and paranasal sinuses by tumours in the sphenoid sinus is less common than invasion of the base of the skull.

Diagnostic Evaluation

The diagnostic investigation of sphenoid sinus malignancy is initiated with plain x-rays of the skull and paranasal sinuses. Although these may be quite informative, hypocycloidal polytomography will generally be needed to confirm and localize the mass, as well as to determine the extent of bony erosion (Banna *et al.*, 1977).

Computerized tomographic imaging of the skull base is invaluable in determining the soft tissue extent of the tumour (Weber *et al.*, 1978). Angiography can play a valuable role in identifying the degree of vascularity of the tumour and its primary arterial supply, as well as revealing significant displacement of neighbouring

TABLE 6. NEUROLOGICAL SIGNS AND SYMPTOMS (OTHER THAN NEURO-OPHTHALMOLOGICAL) RECORDED IN 42 CASES OF PRIMARY SPHENOID SINUS MALIGNANCY*

Symptom of sign		*No. of patients*
Headache		32
Facial pain and/or paraesthesiae (includes cranial nerve V involvement)		12
Cranial nerve involvement (excluding cranial nerve V)		12
I	1	
VII	3	
VIII	2	
IX, X, XI, XII (as group)	5	
'Several cranial nerves'	1	
Involvement of higher intellectual function		5
Personality change	1	
Confusion	1	
Altered consciousness	1	
Coma	2	
Pyramidal tract involvement		3
Hemiplegia	2	
Babinski sign (bilat.)	1	
Meningitis		2
Increased intracranial pressure		2
Gait disturbance		1
'Entire brainstem involved'		1

* No nonneuro-ophthalmological neurological signs and symptoms were reported in 7 cases.

vascular structures (Larsson and Maartensson, 1954; McCarthy and Lawrence, 1975). Lumbar puncture appears to be of limited value. In view of the primarily extradural location and spread of sphenoid sinus tumours it is not surprising that CSF constituents are commonly normal.

In the final analysis, diagnosis will depend upon tissue confirmation by direct open biopsy of the sphenoid sinus. The difficulty in obtaining a tissue diagnosis should not be underestimated, especially if sinus obstruction and infection supervene (Hardie and Ahronheim, 1943). Repeated biopsy should be pursued where suspicion is high.

Treatment and Prognosis

The most common approach to the treatment of all paranasal sinus malignancy has been primary surgery followed by irradiation (Frazell and Lewis, 1963; Lewis and Castro, 1972; Bridger *et al.*, 1978). As virtually 99 per cent of these cases involve either the maxillary (80 per cent) or ethmoid (20 per cent) sinuses this mode of therapy may not be appropriate for the less accessible sphenoid. Accurate evaluation of the treatment of sphenoid cancer requires its identification and analysis within studies of the larger group of paranasal sinus malignancies. This has not been done and may well be impossible because of its obvious rarity. Alternative approaches that are available include conclusions based on the study of all sinus malignancy and the review of treatment of reported individual cases and small series.

Meaningful comparison of available treatment modalities for paranasal sinus malignancy requires controlled trials. These have not been undertaken and are probably impossible in single institutions because of the rarity of sinus cancer. Comparison of treatment between institutions is also difficult because of lack of uniformity both in case material and reporting methods (Bridger *et al.*, 1978). Classification of paranasal sinus malignancy would be helpful but is presently available for only maxillary tumours (Ellingwood and Million, 1979).

Recent studies of irradiation and irradiation followed by surgery provide no definitive answers. Ellingwood and Million (1979) studied 32 tumours involving the nasal cavity, ethmoid and sphenoid sinuses, treated with radical irradiation (60 to 80 grays delivered with Cobalt 60). Only 1 case was of sphenoid origin. They did not recommend either surgical intervention or chemotherapy. Their group achieved 76 per cent local control and 59 per cent actuarial survival at five years. The most valuable feature of their study may be their suggested tumour classification. A three stage stratification, it identified cases by presence or absence of orbital and intracranial extension: Stage I, without orbital extension; Stage II, with orbital involvement; Stage III, involvement of cranial contents, skull base and nasopharynx.

Bridger *et al.* (1978) in a review of 158 cases of paranasal sinus cancer (8 cases were of sphenoid origin) found survival was best when irradiation (50–60 grays delivered either by a Cobalt 60 or 22 MEV Betatron source) was followed by surgery. Their five year survival was 82 per cent for irradiation and surgery while irradiation alone achieved only a 50 per cent result. They admitted to significant bias in case selection which unfortunately casts doubt on the validity of their figures. Nevertheless, they made several interesting and useful observations. First, they found that half of the patients undergoing postirradiation surgery had residual tumour, indicating that increasing tumour bulk decreased the chance of tumour eradication by irradiation alone; secondly, anaemia at presentation appeared to correlate with a poor outcome; and, finally, involvement of regional nodes and distant metastases regularly invoked a poor prognosis. They recommended use of irradiation followed by surgery after correction of anaemia with the exclusion of patients with regional nodes and distant metastases from surgical intervention. They further suggested consideration of chemotherapy in advanced cases.

The value of these reviews in assessing therapy specifically in sphenoid cancer is difficult to determine. Without the independent analysis of sphenoid cases little can be said with confidence. The evaluation of treatment in the cases of sphenoid sinus malignancy reviewed here is complex. Publication of cases occurred over several decades with roughly 25 per cent reported before 1950. Despite this impediment to comparison, a clear trend in treatment is evident. Of the 33 cases in which the mode of treatment was identified, 31 received irradiation of one form or another, 2 in conjunction with surgery and 3 in conjunction with chemotherapy. Where survival was known, most patients with primary sphenoid sinus malignancy lived no more than three years. Of the 42 cases reported, 27 had died within two years. Four had been followed two years or less. Two cases were still alive at six and a half and six years, respectively. Follow-up was unavailable in 9 patients.

Integrating the data available from reviews of treatment of paranasal sinus cancer in general with that obtained from our analysis of treatment instituted in cases of sphenoid origin, it appears that irradiation is the favoured approach. The role of surgery is uncertain, but seems less satisfactory than in tumours in the more accessible sinuses. Adjunctive chemotherapy is probably appropriate in most instances (Carter, 1977; Vogl and Kaplan, 1979). Despite the ominous ultimate outcome, many patients received good palliation with irradiation. Resolution of neuro-ophthalmological signs and symptoms as well as the commonly associated disabling pain was frequent, but often brief.

Conclusions

Primary carcinoma of the sphenoid sinus is a rare malignancy. We have identified and reported 39 cases from the English literature in addition to 3 personal cases. In the data reviewed, the neuro-ophthalmological character of the presentation and course is striking. Three neuro-ophthalmological syndromes of common occurrence were recognized: the sphenocavernous syndrome (20 cases), isolated paralysis of the sixth cranial nerve (8 cases) and optic nerve and chiasmal syndrome (5 cases). Investigation is heavily dependent upon open biopsy. Current therapy utilizes both irradiation and chemotherapy. Surgery appears to have little to offer for this inaccessible tumour. Although good palliation is often achieved, the ultimate outcome is unsatisfactory with a 93 per cent mortality rate at two years. Carcinoma of the sphenoid sinus should be considered in the differential diagnosis of isolated abducens paralysis and sphenocavernous or chiasmal syndromes of obscure origin.

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(*Received August 25, 1983. Revised January 17, 1984*)

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A DESCRIPTIVE STUDY OF THE BLOOD VESSELS OF THE SCIATIC NERVE IN THE RAT, MAN AND OTHER MAMMALS

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SUMMARY

The gross blood supply and internal vascular organization of the sciatic nerve in the rat (and other mammals including man) have been studied by injection, dissection, and microradiographic methods, in thick sections stained for alkaline phosphatase and semithin sections, and by electron microscopy.

In the rat, an anastomotic vascular connection from the arteria comitans to the medial femoral circumflex artery is illustrated. In all species studied, the microvascular network of the nerve has an unusually large calibre and wide spacing, particularly when compared with that of skeletal muscle. Arterioles and venules are present within fascicles; the arterioles are thin-walled, with only rudimentary internal elastic laminae. Endoneurial capillaries are large, continuous and nonfenestrated, with prominent (often multiple) basal laminae and an unusually complete pericyte investment. Endothelial junctions appear to vary in type; not all are tight. Pinocytosis is common.

The extensively interconnected vascular network of the nerve fascicle may act as an adaptable *in situ* reservoir for blood in the precise maintenance of the endoneurial milieu.

INTRODUCTION

The blood vessels in peripheral nerves operate under and help to maintain specialized conditions of pressure and ionic balance. They also display a blood-nerve barrier similar but not identical to that in the central nervous system. In these circumstances it seems unwise to take for granted that they constitute an ordinary vascular bed. This study was undertaken to establish a detailed anatomical basis for observations of intraneural vascular function and pathology.

Previous studies describing the blood vessels within nerves have concentrated on identifying their sources of supply, in testing their competence under various conditions, and in testing their permeability with dyes and particulate tracers (Adams, 1942; Sunderland, 1945, 1968; Lundborg, 1970, 1975). *In vivo* observations of the supplying and intraneural vessels have been made by Roberts *et al.* (1950) in frogs, small mammals and rabbits, and Lundborg (1970) in the rabbit. Investigations into vascular permeability in the nerve have been undertaken and reviewed by Waksman (1961) and Olsson (1975). Ischaemia of peripheral nerves has been studied by Weddell and Sinclair (1947), Richards (1951), Hassler (1969), Lundborg (1970) and Sjöstrand *et al.* (1977). Ishikawa (1959) and Marcarian and Smith (1968) made some measurements of the vessels in cat nerves; otherwise, quantitative information about the size or distribution of intraneural vessels is scarce and anecdotal. Nerves have been variously described as having great numbers of small vessels or relatively poor vascularization.

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The mammalian intraneural circulation originates with nutrient arteries arriving at intervals along the length of the nerve; these then bifurcate into ascending and descending branches which join an extensive epineurial network of longitudinal arterioles and venules with many anastomotic connections. Emerging veins are usually paired with the arteries. Smaller vessels run inside the single or multiple fascicles, and are similarly organized in longitudinal networks with cross connections. The vessels running obliquely through the perineurium to connect the vascular networks inside the fascicles with those situated outside in the epineurium have been described by Lundborg (1979). *Intraneural* refers to the vessels contained in all layers of the nerve (epi-, peri-, and endoneurium), *intrafascicular* or *endoneurial* only to those inside the fascicle in the endoneurium.

While they are vulnerable to stretching tension, these intraneural networks have such an extraordinary adaptability and competence under a wide range of conditions that it is difficult to produce ischaemic lesions experimentally (Lundborg, 1970; Lundborg and Brånemark, 1968; Olsson, 1972; Sjöstrand *et al.*, 1977; Miyamoto *et al.*, 1979). Surgically, nerves appear to maintain a good circulation even after extensive mobilizations, but conservative handling is usually recommended, and Lundborg (1979) observed that microsurgical techniques, which now permit delicate fascicle-by-fascicle suturing, risk increased damage to the epineurial vessels running between the fascicles.

There are differing reports about specific permeabilities of intrafascicular vessels in various mammals (Waksman, 1961; Olsson, 1975; Arvidson, 1977), but agreement appears general that the blood-nerve barrier is more variable from animal to animal (and even from one fascicle to another in the same nerve) than the blood-brain barrier, and that the two barriers are differently affected by certain substances, e.g. histamine (Olsson, 1966; Malmgren and Olsson, 1980; Powell *et al.*, 1980; Gross *et al.*, 1981). The blood-nerve barrier in the rat is thought to be relatively tight (Dyck *et al.*, 1980), but Waksman (1961) saw, and Oldfors and Sourander (1978) postulated a slight leakage. There is no question of a comparable barrier function in epineurial vessels; tracers readily pass through them into the surrounding connective tissue, and fenestrations and open junctions have been observed (Olsson, 1975).

Dorsal root ganglia and nerve roots differ interestingly from the rest of the peripheral nervous system in that their vessels lack a barrier, displaying fenestrations and behaving like the 'leaky spots' of the brain (Brierley, 1955; Waksman, 1961; Olsson, 1968; Olsson *et al.*, 1972; Jacobs *et al.*, 1975, 1976). Tracers that leak from the vessels into these areas do not seem to pass further along the nerves; the mechanism of this restriction is not understood, nor is it known whether it applies to natural substances.

Axons depend on remote cell bodies for much of their nourishment and maintenance; intrafascicular vessels nourish primarily the endoneurial connective tissues and Schwann cells. These vessels, assisted by the tight perineurial seal around the fascicles, are also responsible for maintaining the balanced humoral milieu that supports the rapid, complicated and repeated ion exchanges on which nerve function depends (Boddingius *et al.*, 1972; Lundborg, 1975; Sjöstrand *et al.*, 1977). Disruption of the integrity of either perineurium or endothelium lets in an 'environmental draught' that interferes with neural function (Morris *et al.*, 1972; Gentili *et al.*, 1980).

The present study describes the pattern of nutrient and intraneural vessels of the rat sciatic nerve using injection, dissection and microradiographic methods. In addition, the alkaline phosphatase staining technique was applied to thick frozen sections to outline the intrafascicular vascular networks, and to display the distribution of the enzyme itself along the vascular tree. Semithin (1 μm) and ultrathin Araldite sections were used to examine the structure of the walls of vessels. Where possible, comparisons of nerves from other laboratory mammals and man were included. Comparisons were made with the microvascular network in adjacent skeletal muscles, since this tissue is anatomically and functionally related to nerve and has a 'typical', dense and well-studied capillary bed.

In a concurrent morphometric study (Bell and Weddell, 1984), intrafascicular vessels of nerve and endomysial vessels of skeletal muscle were studied and compared in semithin sections with a Quantimet 720 image analyser.

METHODS

Injection, Dissection and Microradiography

Twenty-four white rats of various ages and both sexes were used. They were anaesthetized with pentobarbitone sodium (Nembutal) or tribromoethyl alcohol (Avertin), and heparinized and, before Micropaque injections for capillaries, vasodilated with sodium nitrite. The injections were carried out with hand pressure on a syringe through a plastic canula inserted into the thoracic aorta. The vascular field was usually flushed with 50 ml of warm saline before switching to the opaque medium. Vascular filling was monitored by watching intestinal organs and toes. The pelvis and hind legs were fixed intact in 10 per cent formal saline.

All injection media were radiopaque, suitable for visual or x-ray examination, and were injected warm (50° C). Preparations in which major vessels and capillaries were to be filled were injected through their arterial supply with 25 per cent liquid white Micropaque (Damancy and Co., Ware, Herts.) in 2 per cent gelatin until the arterial system, capillary beds and veins appeared well filled. To distinguish arteries from veins, Chromopaques (Colorpaques, Damancy) were used. Blue Chromopaque (40 per cent in 2 per cent gelatin) was injected into the arterial system until it had gained the veins (presumably *via* thoroughfare channels and larger capillaries; the general capillary beds did not fill). This was followed by more concentrated yellow Chromopaque (80 per cent in 2 per cent gelatin with a neutral medium : water ratio of 1 : 3), which displaced the blue medium in the arteries and arterioles but was too viscous to penetrate further. The resulting preparation showed yellow arteries and blue veins, which could also be differentiated radiographically since blue Chromopaque is more radiopaque, even when more dilute. The larger calibre of the veins increased their differential x-ray absorption still further. (This method of 'chasing' one coloured medium with another, suggested by Professor R. L. Saunders, is useful in femoral vessels where valves make retrograde venous injections undependable.)

Dissections were performed under a Zeiss operating microscope. The sciatic nerve and its major nutrient vessel systems were exposed from the lateral aspect of the thigh (fig. 1). (A few injected specimens were cleared with methyl salicylate in various stages of dissection. The tissues became transparent and turned brown; vascular patterns became visible in depth and *in situ*, the yellow and blue media providing better contrasts than the white Micropaque.) Drawings were made and photographs taken.

For microradiography, the sciatic nerve in the thigh was removed along with the underlying part of the caudofemoralis muscle (still attached to the nerve by the posterior mesoneurium). The muscle was thicker than the nerve; to equalize x-ray absorption the muscle was thinned by trimming, avoiding major internal vessels. These preparations were spread carefully on a thin plastic film (Melinex, type S, 23 μm, ICI Plastics Division, Welwyn Garden City, Herts.), covered with a second piece of plastic, sandwiched between two glass slides, secured with a rubber band, and stored in 10 per cent formalin.

Microradiographs were made with the assistance of Mr R. V. Ely on his custom-built E15M and WXM30 x-ray microscopes at the Wardray Company, Sandford, Oxon, and Reading University. (The theoretical principles, medical applications and descriptions of these machines are given in Saunders and Ely, 1966; Saunders, 1967, 1973; Ely, 1980). Exposures made with a tungsten target at 20–30 kV (source size 5 to 10 μm) were recorded on N7E50 Ilford film for large specimens, and Ilford and Kodak H R Plates (2 × 2 in) for smaller pieces. It was possible to resolve injected capillaries. Some stereo exposures were made. Vacuum chambers were not used; specimens were drained and radiographed wet, supported by Melinex film.

Alkaline Phosphatase Histochemistry

Sciatic nerves and related muscle tissue from 1 black and white and 9 white rats, 5 white mice, 2 cats, 1 rabbit, 1 guinea pig, and 3 humans were used. The animals were killed just before tissue removal with an overdose of anaesthetic, or were under deep anaesthesia. The human specimens were taken at autopsy from 1 male and 2 females (aged 40 to 82 years) who died without evidence of neurological disease.

In the animals, the sciatic nerve was removed from the hip to the knee, often with the anterior biceps femoris or caudofemoralis muscle ('white' muscles, with minimum capillary densities). Fixation was in a weak, cold (4° C) formalin-calcium solution adjusted to neutral pH with KOH. Longitudinal 100 to 200 μm frozen sections were cut on a Leitz freezing microtome with electric cooling. Sections were collected in cold distilled water. They were incubated and converted in solutions modified by Bell and Scarrow (1984) from the original Gomori metallic method, substituting lead nitrate for cobalt nitrate; the resulting black vessels have a striking yellow background.

Semithin (1 μm) and Ultrathin Sections

Sciatic nerves and related muscle tissue (usually anterior biceps femoris) from 25 white rats, 2 cats, 1 white mouse, 1 rabbit, and 1 Rhesus monkey were used; all were adult animals. The rats were anaesthetized with Nembutal. Under the operating microscope two adjacent segments of sciatic nerve were removed (3rd to 5th mm below departure of the posterior division of the nerve), along with three pieces from the top, middle, and bottom of the anterior border of the anterior biceps femoris muscle (each approximately 1 mm^3). Dissection and fixation (by immersion in a modified 3 per cent glutaraldehyde solution, Perrachia and Mittler, 1972) were at room temperature. The pieces were postfixed in 2 per cent osmium tetroxide, processed through alcohols and epoxy propane and embedded in Araldite. Dissection and fixation for animals other than the rat were not standardized since the material was obtained from terminal experiments in other laboratories; subsequent treatments were similar to those for the rat.

Semithin and ultrathin transverse sections were cut on an LKB Ultrotome III. The 1 μm sections were stained with toluidine blue and basic fuchsin, the ultrathin sections with uranyl acetate and lead citrate. The latter were examined in a Siemens Elmiskop 101. Ultrathin sections were not taken from all specimens; more 1 μm than ultrathin sections were examined.

RESULTS

Gross Vascular Anatomy

Two major recognized arteries (with their accompanying veins) serve the sciatic nerve of the rat thigh: (1) the inferior gluteal artery, giving rise to the arteria comitans (nervi ischiadici) in the posterior mesoneurium, and (2) the popliteal artery, which reaches the nerve at the knee and branches variably up and down the nerve and its branches (Greene, 1968; Siu and Fahrer, 1974). The microradiographs and dissections of this study revealed, in about half of the rats examined, an intermediate artery and vein, equivalent in size to the other supplying vessels, joining the sciatic nerve about halfway down the thigh (figs. 1, 2). The artery is comparable to the anastomotic branch in man joining the medial femoral circumflex with the inferior gluteal artery and its branches; it therefore seems appropriate in the rat to call these vessels the anastomotic artery and vein.

Intraneural Vascular Patterns and Structure

Clearing and microradiography. In both cleared and radiographed specimens, the longitudinal network of arteries and veins and their connections were easily recognized in the epineurium and in the intrafascicular compartment (fig. 2). The pattern closely resembled those reported for the dog and rabbit by Nobel (1969), Lundborg (1970), and Nobel and Black (1974). It was so striking that in cleared preparations, where distinctions between all tissues disappeared, the obvious bundle of long, relatively large coloured vessels was the only feature identifying the sciatic nerve. The distinction between arterial and venous vessels, however, even in the two-colour injections, was clear only down to the calibre of the comitans, anastomotic and popliteal vessels, not beyond. Within one long intraneural vessel the colour or radiodensity of the contents might change abruptly, sometimes more than once. Inappropriate colours were found in vessels that were otherwise identified by their course as arteries (wavy) or veins (straight). Artefacts of injection may produce similar confusing patterns, but in other tissues of these preparations arteriolar and venular separations were clear and unambiguous. Erratic filling might equally be the result of arteriovenous anastomoses (recognized in the rabbit by Roberts *et al.*, 1950, and Lundborg, 1970), or the directional ambiguity of intraneural vascular patterns that allows reversal of flow; both are features that contribute to the extraordinary competence and adaptability of this circulation. Lundborg reported that there were as many vessels carrying blood up the nerve as down, and in these rat preparations it was not possible, without external identifying landmarks, to tell by the vascular pattern which end of an isolated nerve was proximal. Caution is justified when identifying arterial and venous vessels in the nerve on the basis of differential injections.

The discrepancy in size and distribution density between the smallest vessels within the nerve and those in the adjacent skeletal muscle first became clear in high resolution microradiographs (fig. 3). The Micropaque injection medium delineates a closer-meshed network of smaller vessels in the well-filled areas of muscle than in the nerve.

Alkaline phosphatase. The wide spacing and large size of intrafascicular vessels was also well illustrated in thick alkaline phosphatase sections (fig. 4). Subsequent measurements (Bell and Weddell, 1984) showed that the average diameter of the small endoneurial vessels in the rat was 8.8 μm while that of the muscle capillaries was only 5.2 μm. On average, the tissue area per vessel in the transverse section of nerve

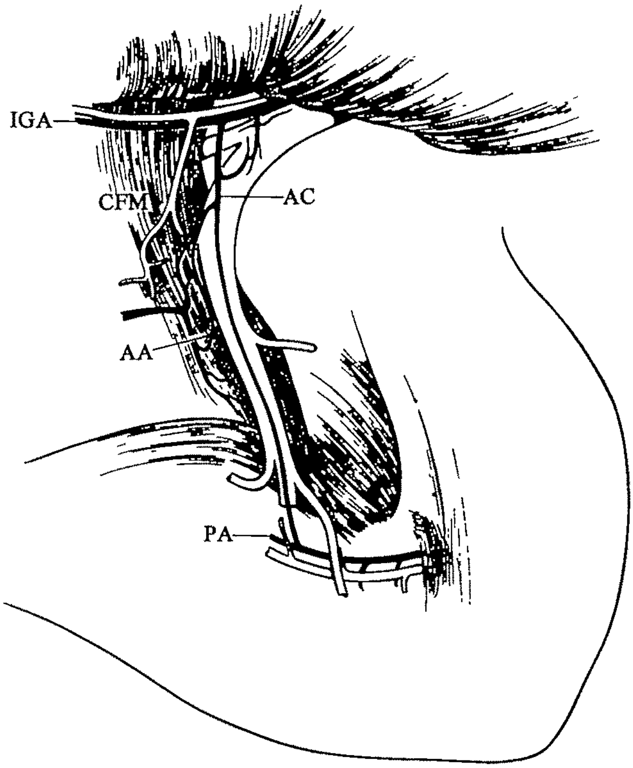

FIG. 1. Major vessels of the sciatic nerve in the right thigh of the rat, lateral exposure, with gluteal and biceps femoris muscles reflected upwards. Arteries are black; accompanying veins are partially shown in white. At the top, the inferior gluteal artery (IGA) gives rise to the arteria comitans (AC), which breaks up into a network of arterioles in and around the nerve, linking eventually with branches arising from the popliteal artery (PA) at the knee (*bottom*). In many specimens, the AC also sends a branch to link with an anastomotic artery (AA) that arises from branches of the medial femoral circumflex artery on the medial side of the thigh. The AA actually arises within the substance of or behind (medial to) the caudofemoralis muscle (CFM), but for simplicity it is depicted on the surface (*see* fig. 2). (Drawing, G. Moogk, after C. Court.)

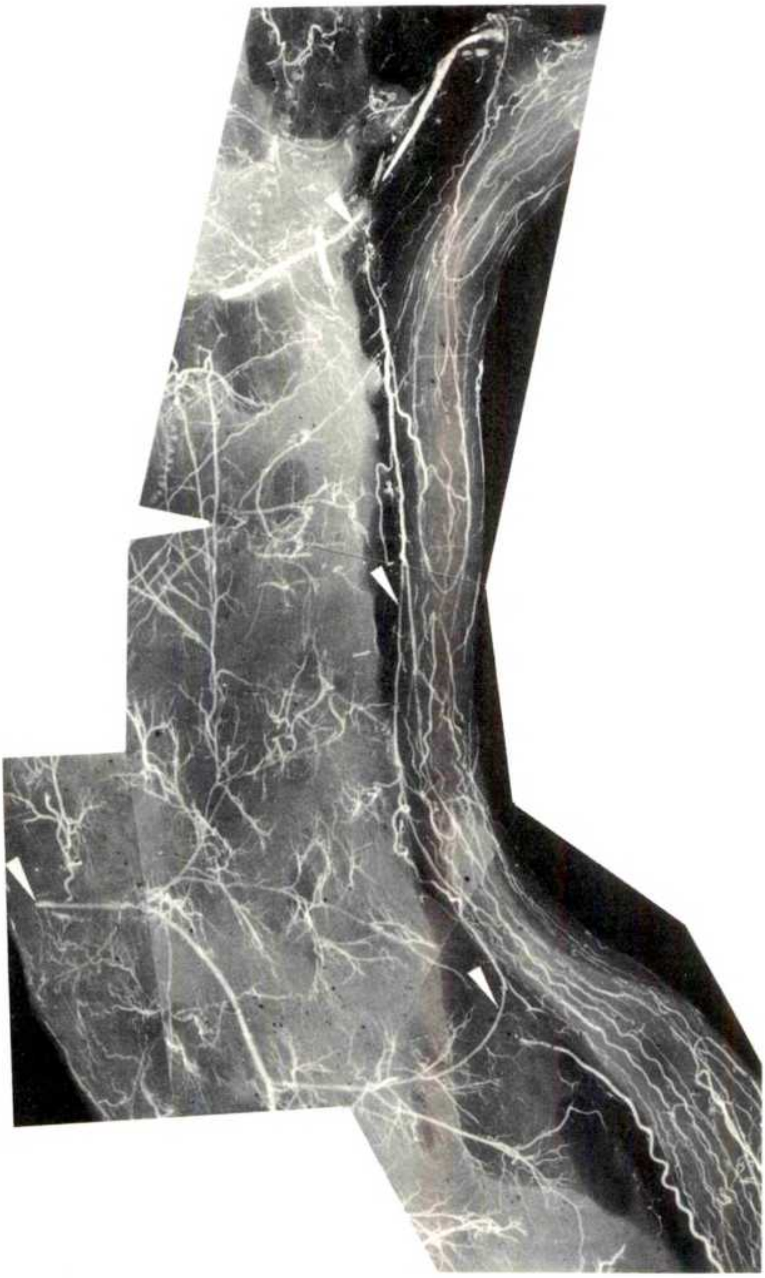

FIG. 2. Contact microradiograph (Kodak high resolution emulsion) of the sciatic nerve and its longitudinal vascular network (at *right*), and the caudofemoralis muscle (*left*). The four small white arrowheads mark (from the *left*) the course of the anastomotic artery as it arises in the muscle, emerges from the anterior muscle border, and joins the arteria comitans along the posterior surface of the nerve, and also, at the top, the origin of the arteria comitans from the inferior gluteal artery. Compare with fig. 1. Micropaque injection. (× 9.)

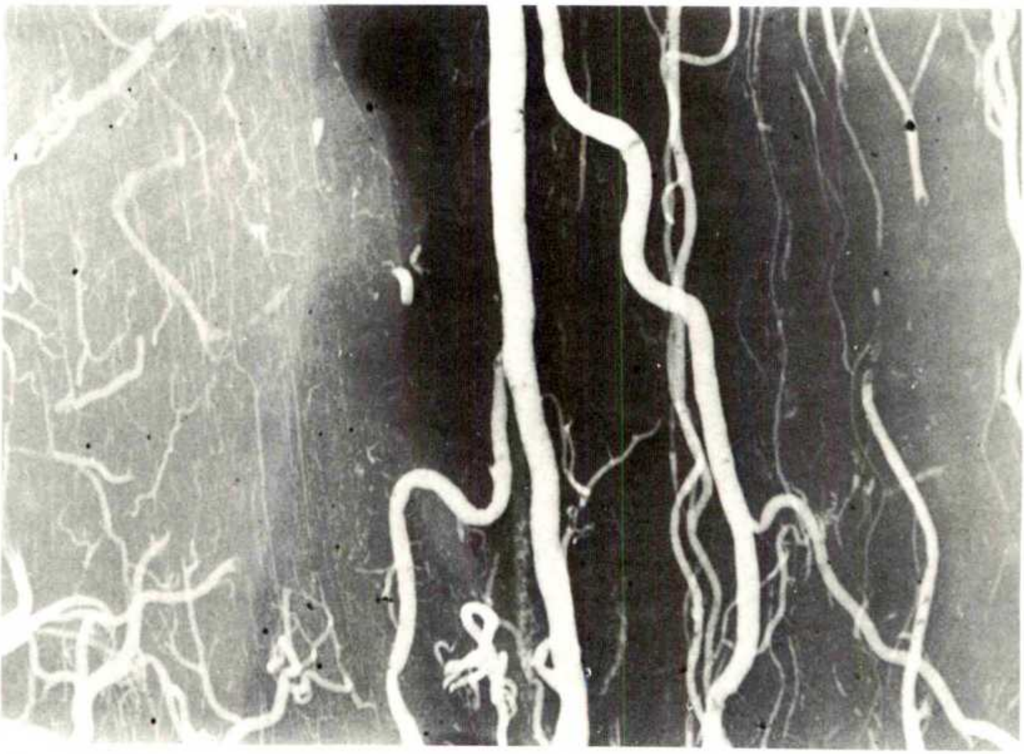

FIG. 3. Contact microradiograph (Kodak high resolution emulsion) of rat sciatic nerve (*right*) contrasted with caudofemoralis skeletal muscle (*left*). The muscle shows greater numbers of fine closely packed vessels than the nerve. Micropaque injection. (× 60.)

(i.e. the total cross-sectional area of the fascicle divided by the number of vessels present) was 2.5 times larger than in the muscle. Fig. 5 compares alkaline phosphatase preparations of the nerve and muscle capillaries of the rat, cat, guinea pig and man. The sciatic nerve from the mouse gave a similar impression. Preparations of rabbit sciatic nerve showed no vascular alkaline phosphatase activity at all (confirming Hennig, 1972); rabbit cerebral vessels are also negative (Newman *et al.*, 1950; Torack *et al.*, 1967; M. A. Bell, unpublished observations). These examples suggest that the discrepancy between the vessels of nerve and muscle is common to several species, including man. Minor variations occur: the endoneurial vessels in the cat and guinea pig appear slightly closer together than those of the rat and the man. In man, comparison with the microvascular pattern of the cerebral cortex emphasizes the large size and sparseness of the neural vessels (fig. 6).

Very small intrafascicular vessels, the same size as capillaries in muscle, did appear occasionally in the rat, and slightly more often in the cat and man. The network of intrafascicular vessels lends itself to interesting complexities and looping

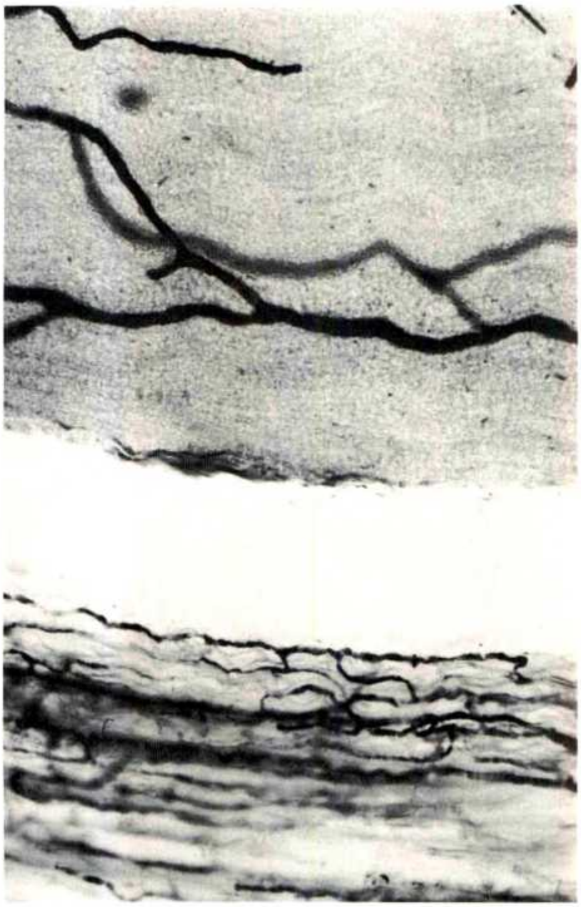

FIG. 4. Alkaline phosphatase preparations (200 μm frozen section) of the vessels in rat sciatic nerve (*above*) contrasted with those in skeletal muscle (*below*). The close mesh of small vessels in the muscle represents a 'typical' capillary bed; the large size and wide spacing of the nerve's microvasculature is striking. (× 154.)

patterns, particularly in man (fig. 7A); none of these gave any indication of the direction of blood flow or the proximal-distal orientation of the nerve.

In all the animals (except the rabbit), and in man, vascular phosphatase activity began in the small intrafascicular arterioles, often with the abrupt 'cuffing' at the origin described in the arterioles of rat skeletal muscle and brain by Romanul and Bannister (1962) and Bannister and Romanul (1963) (fig. 7B). The smallest vessels in the nerve, although appreciably larger than 'typical' capillaries, stained continuously and uniformly; this reaction is characteristic of capillaries in other tissues. If it were not for their positive phosphatase reaction, these smallest neural vessels might have been taken for postcapillary venules, which they resembled in size and wall structure. Postcapillary and larger venules, however, in all other tissues so far examined, show no phosphatase activity; the stain fades at the venous end of the capillary bed. This may also happen in the nerve, but faint unstained postcapillary and larger venules, readily demonstrable in other tissues, appeared only rarely in the

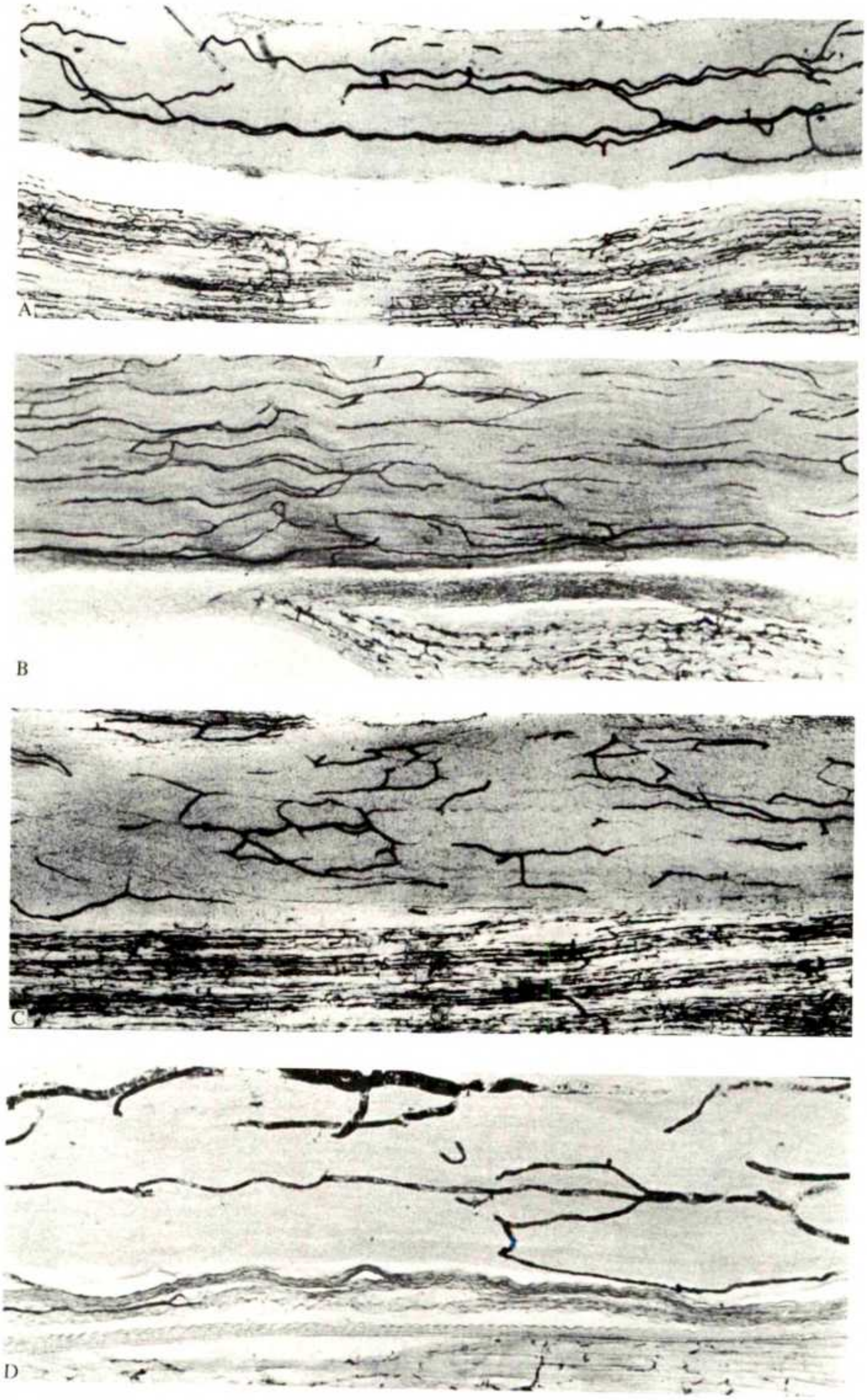

FIG. 5. Alkaline phosphatase preparations (200 μm frozen sections) of vessels in sciatic nerves (*above*) and skeletal muscles (*below*) of different species: A, rat; B, cat; C, guinea pig; D, man. (× 38.)

phosphatase sections of nerve (fig. 7C). It is not clear why: semithin and ultrathin transverse sections clearly showed intrafascicular venules up to 30 μm in diameter.

Alkaline phosphatase preparations were also used to demonstrate the vascular pattern of rat spinal cord, cauda equina, nerve roots and ganglia (fig. 8). The cord showed its recognized pattern of small capillaries, denser in grey matter than in white, while the cauda equina and nerve roots had larger sparsely distributed vessels, in size and spacing resembling those in the rest of the peripheral nervous system. At higher magnifications, large well-stained vessels were also apparent in the ganglia, curling and twisting with remarkable density so that each ganglion cell seemed to be adjacent to one or more vessels. This appearance has been confirmed in electron micrographs (A. G. M. Weddell, unpublished observations). A microradiograph of injected human fetal spinal ganglia shown by Saunders (1960, 1980) gives the same impression of large, densely packed vessels.

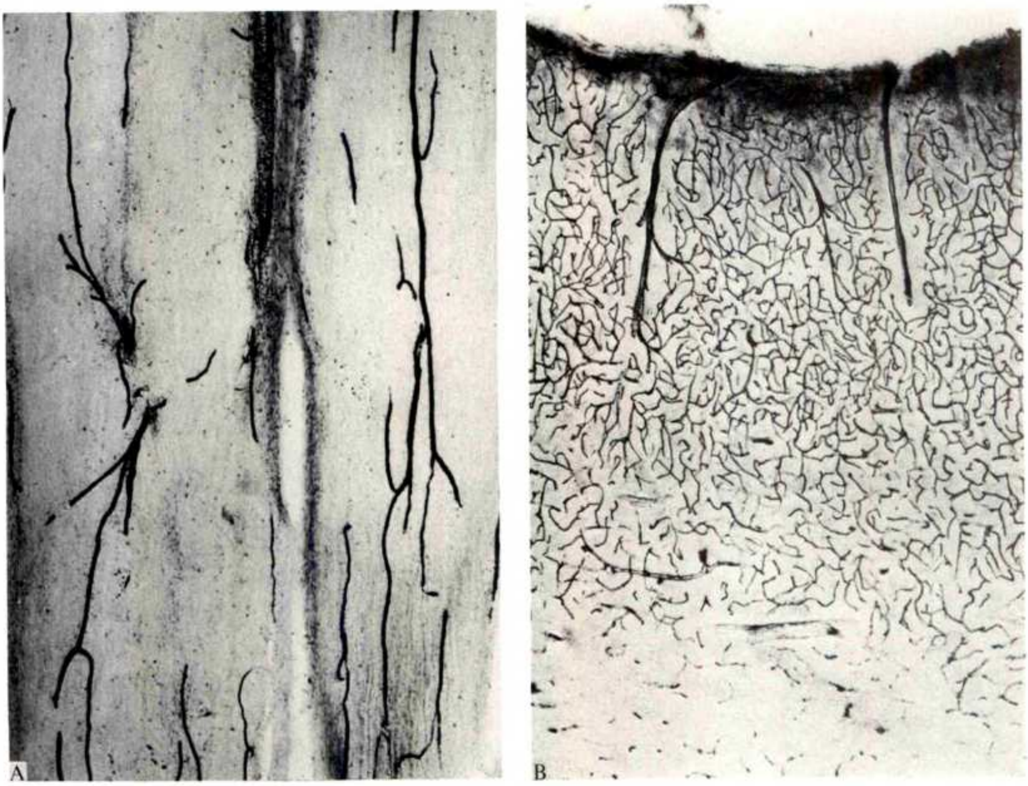

FIG. 6. Alkaline phosphatase preparations (100 μm frozen sections) of the large, widely spaced vessels in human sciatic nerve (A) contrasted with the smaller, denser ones in human cerebral cortex (B). Both pictures are the same magnification. (× 30.) In B, the cortical arterioles show strong alkaline phosphatase activity from the pial surface inwards. A short horizontal fragment of a large unstained venule is visible at the junction of cortex and white matter where the capillary density falls off.

Semithin and ultrathin sections. Majno (1965), White and Clawson (1967), Sunderland (1968), Breathnach (1971) and Rhodin (1974) have established descriptions for the terminal vessels of the 'typical' vascular tree in a wide range of tissues and animals. Their criteria have been used in this study.

The largest intrafascicular vessels encountered in the rat were arterioles and venules with diameters of 25 to 30 μm. In 1 μm sections examined by light microscopy the arterioles seemed thinner walled than those of comparable size in the epineurium, and when dilated were difficult to distinguish from the venules. They did, however, consistently show a three-layered appearance: (1) a continuous dark (blue) outer layer (by electron microscopy seen to consist of a single layer of muscle cells); (2) the pale basement membrane space, wide and clearly defined (filled with the often complex basal laminae of the muscle and endothelial cells, and

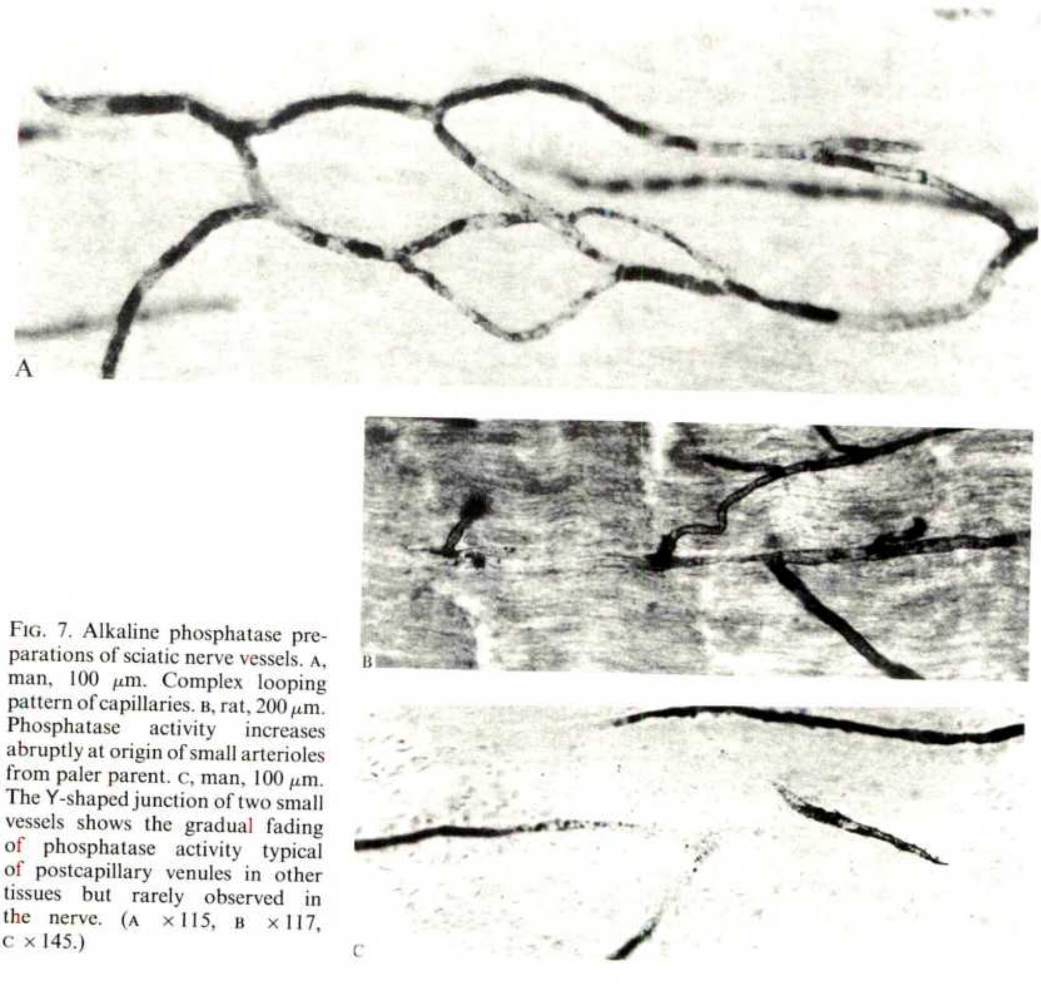

FIG. 7. Alkaline phosphatase preparations of sciatic nerve vessels. A, man, 100 μm. Complex looping pattern of capillaries. B, rat, 200 μm. Phosphatase activity increases abruptly at origin of small arterioles from paler parent. C, man, 100 μm. The Y-shaped junction of two small vessels shows the gradual fading of phosphatase activity typical of postcapillary venules in other tissues but rarely observed in the nerve. (A ×115, B ×117, C ×145.)

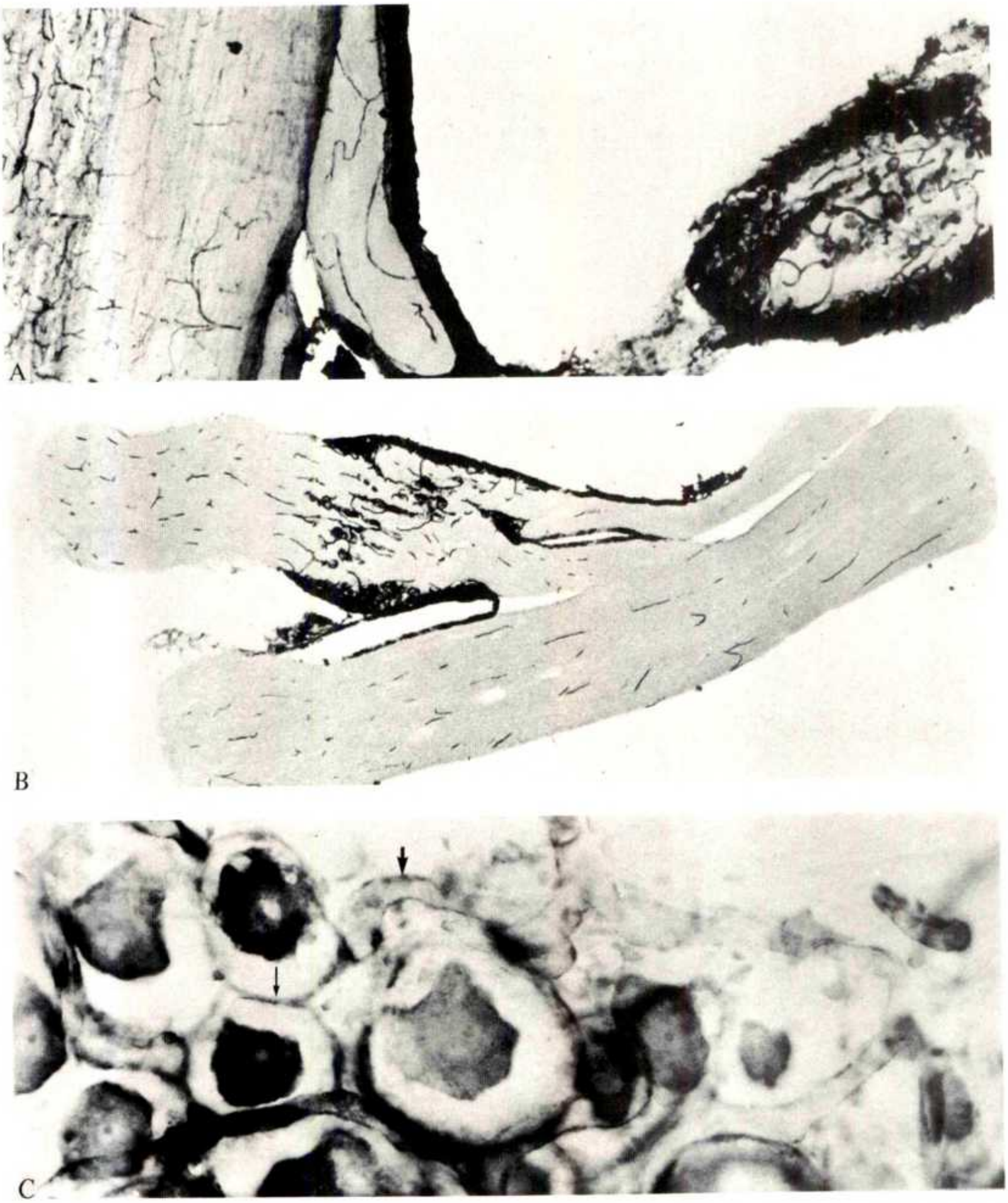

FIG. 8. Alkaline phosphatase vascular preparations (100 μm frozen sections) from the rat. A, in longitudinal section, the spinal cord (*left*) shows 'typical' small capillaries, denser in grey matter than in white. The posterior nerve root has relatively large, widely spaced vessels like those of the sciatic nerve; the attached dorsal root ganglion (*right*), partly obscured by the heavy staining of its capsule, shows a dense network of large vessels around the neurons. (×38.) B, a longitudinal section of cauda equina and attached dorsal root ganglion leading in from a peripheral (sacral) nerve, shows relatively large vessels, widely spaced except for the clustering about ganglion cells. (×20.) C, in a dorsal root ganglion (with neutral red and safranin counterstain), wide capillaries loop around the neurons (thick arrow). The satellite cells of the ganglion are also alkaline phosphatase positive; they form dark capsules around the neurons (thin arrow) which should not be confused with vessels. (×432.)

occasionally with fragments of elastic lamina); and (3) next to the lumen a thin dark (blue) line with occasional nuclear thickenings (endothelium) (figs. 9, 10). The venules showed, by light and electron microscopy, a continuous endothelium, but the middle basement membrane space and outer cell layer, unlike those in the arterioles, were thin, variable and discontinuous (figs. 9, 11). It was not clear whether the cells in the outer layer of the venules were pericytes or smooth muscle cells; they are therefore called periendothelial cells.

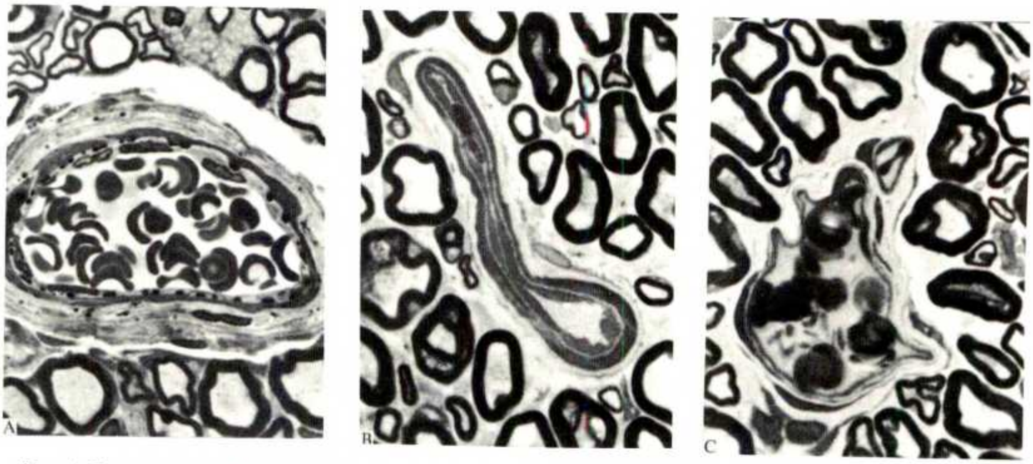

FIG. 9. Transverse 1 μm sections of rat sciatic nerve. A and B show arterioles: the single muscle cell layer is continuous in each case. In A, dark rudimentary patches of internal elastic lamina separate endothelium from muscle. C shows a venule: the periendothelial cells do not form a continuous layer. (× 1000.)

In electron micrographs, arteriolar endothelium tended to be thicker than venular, with longer and more tortuous endothelial junctions. Arterioles had heavier and more tortuous basal laminae; those of the venules were thin and often reduplicated, particularly where exposed by a gap in the outer cell layer. Even when unclear in the light microscope, an arteriole's outer muscle cell layer could be seen by electron microscopy to be complete, whereas a venule's periendothelial coat was discontinuous. The small venules often showed collagen fibres in the space between endothelial and periendothelial layers and frequent contacts (possibly of gap junction type) between endothelial and periendothelial cells (fig. 11); neither feature was seen in arterioles.

The internal elastic laminae of even the large endoneurial arterioles were only fragmentary, less complete than those of epineurial arterioles of equivalent size. In 1 μm sections they appeared as dark dots within the pale basement membrane space (fig. 9A). In electron micrographs these fragments were seen as spaced aggregates of a pale amorphous substance containing darker spots and surrounded by dark dots that probably represent fine fibrils, transversely sectioned. Separate fibrils, lying apart in the basal lamina space, sometimes had tubular profiles (fig. 12). It is not known whether this discontinuous state represents an 'immature' condition (Haust *et al.*, 1965; Fyfe *et al.*, 1968), or simply demonstrates the manner in which all elastic laminae diminish along arterial trees. In considerably smaller arterioles in skeletal muscle, the elastic lamina remnants were similar in texture, but more ragged than their smooth, oval endoneurial counterparts.

The capillaries in muscle preparations matched standard descriptions, having diameters of 3 to 6 μm, a nonfenestrated endothelial cell layer with basal lamina, and sometimes a partial outer covering of pericyte processes (fig. 13). In contrast, the smallest vessels commonly seen in the endoneurium had diameters between 6 and 10 μm, basal laminae (occasionally multiple) and an extensive or even complete pericytic covering (fig. 14). Bennett *et al.* (1959) suggested that a true capillary has a less than 50 per cent investment by pericyte processes; more than that indicated that the vessel is probably a postcapillary venule. Almost all the smallest intrafascicular vessels seen here fit the description of postcapillary venules more closely than that of true capillaries but, for reasons outlined in the Discussion, the term capillary was retained.

Interendothelial junctions in the capillaries were difficult to classify. Tight junctions (pentalaminar, with outer leaflets fused), punctate tight junctions (outer leaflets sealed only at points) and gap junctions (outer leaflets closely approximated, but with a narrow space and some amorphous darkening between) were all seen, as well as some types that appeared to be intermediate or mixed (e.g. a gap junction with one punctate tight spot) (*see* figs. 12B, 15). All types showed some darkening of adjacent cytoplasm. In endoneurial vessels pinocytosis was only slightly less extensive than in muscle vessels. Vesicles were seen in endothelial and smooth muscle cells, and pericytes (figs. 10 to 15). In some instances vesicles in both endothelial and periendothelial cells seemed more numerous on the outer (abluminal) surfaces (*see also* Majno, 1965). In some endoneurial venules the vesicles of periendothelial cells were smaller than those of endothelium. Direct vascular innervation in the endoneurium was not demonstrated; in contrast, transversely sectioned unmyelinated nerve fibres running in the collagenous adventitia of several very small arterioles in skeletal muscle sections were found without difficulty. In the rat, direct innervation apparently follows intraneural vessels into the perineurium (one example seen), but rarely beyond. The endothelial cells of nerve vessels had more and smaller mitochondria than those of skeletal muscle (as do rat brain capillaries, Bradbury, 1976). Fenestrations were not found in endoneurial vessels; one was seen in an epineurial capillary (*see also* Olsson and Reese, 1971).

In the small number of semithin sections prepared from other animals, characteristics of endoneurial vessels resembled those of the rat. In the mouse, all the vessels were strongly dilated and it was impossible to distinguish arterioles from venules. The monkey and the rabbit, more often than the other animals, showed a

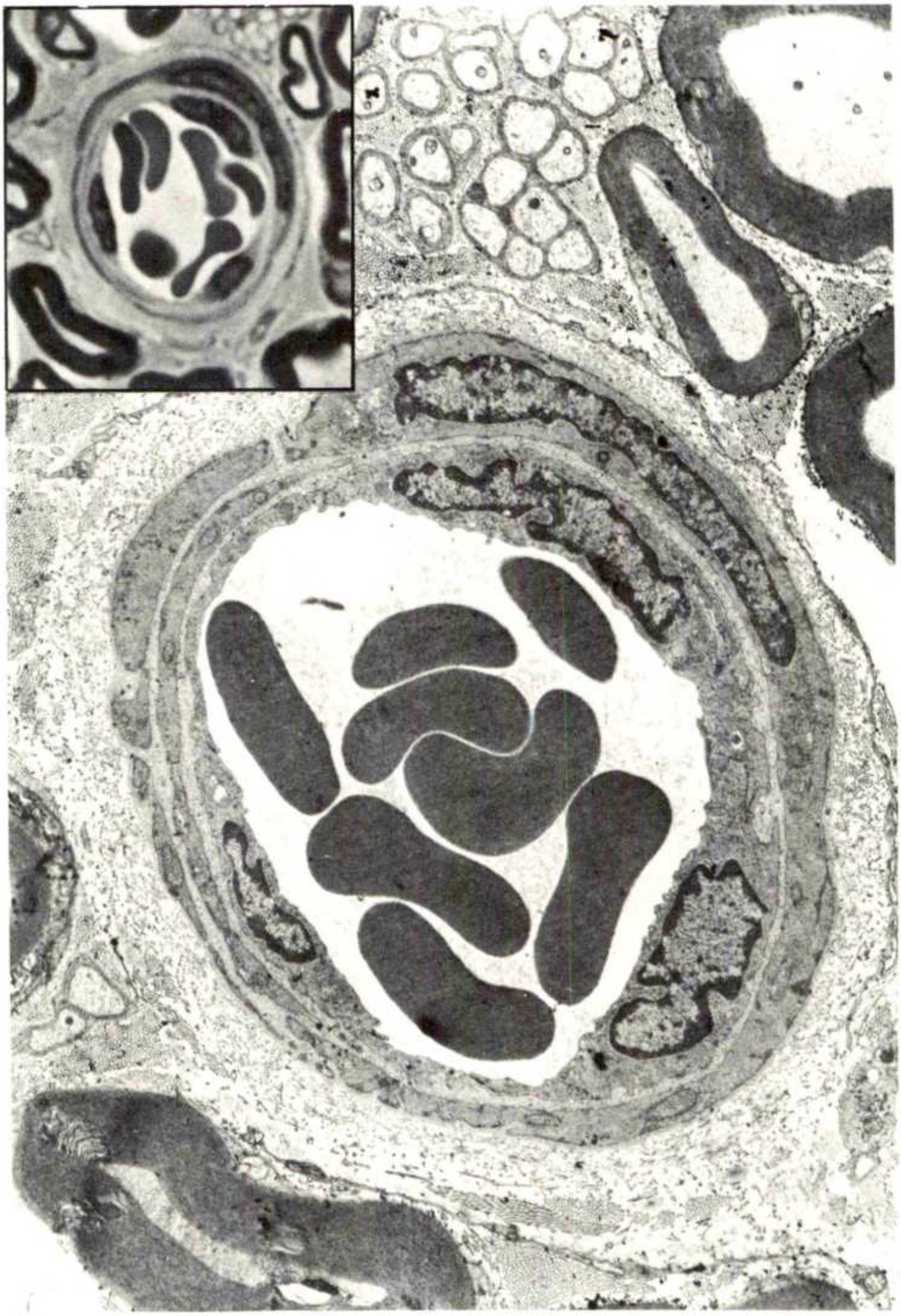

FIG. 10. Arteriole in transverse section of rat sciatic nerve. The electron micrograph shows the continuity of the muscular layer and the absence of any obvious elastic lamina. The *inset* demonstrates the same features in a 1 μm section of the same arteriole. (× 7200; inset × 2300.)

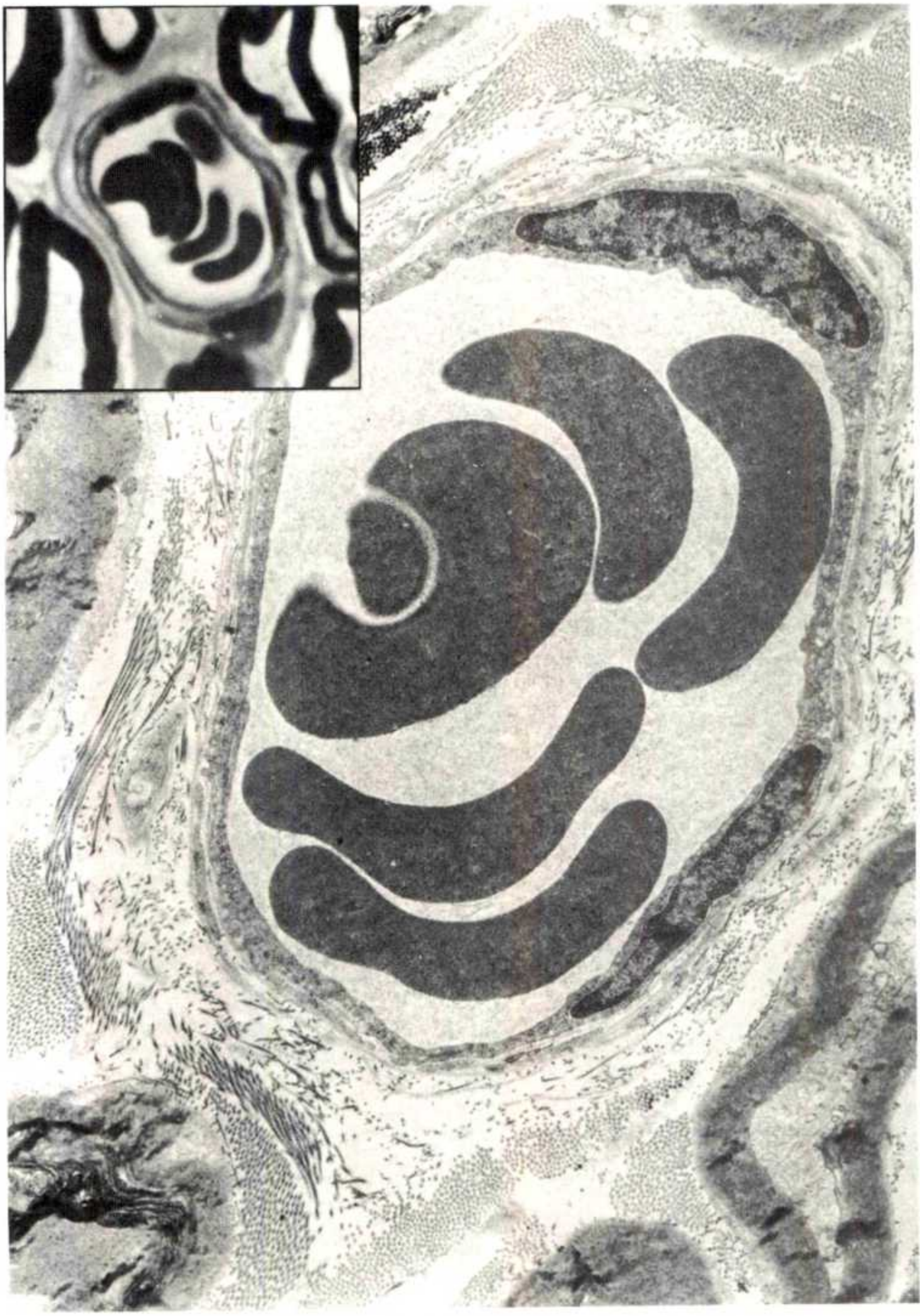

FIG. 11. Venule in transverse section of rat sciatic nerve. The electron micrograph shows that the periendothelial cell layer is incomplete. Collagen fibres may impinge directly on the endothelial basal lamina. The same venule in a 1 μm section is shown in the inset. (× 10 000; inset × 2100.)

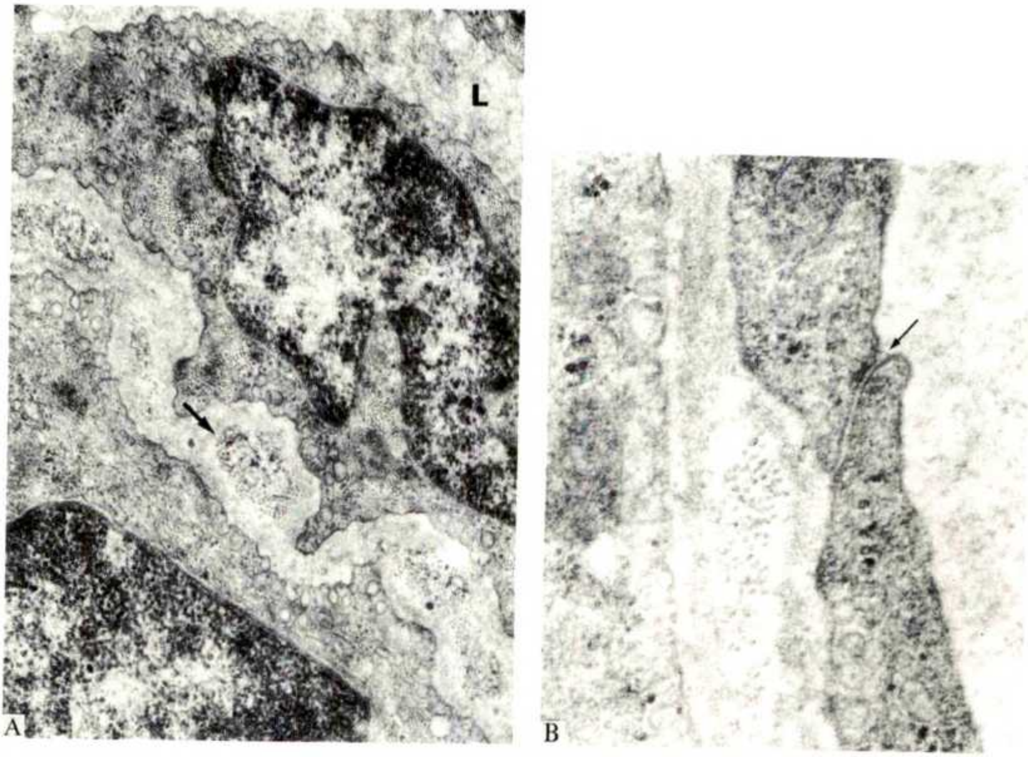

FIG. 12. Electron micrographs from two arterioles in rat sciatic nerve. A arrow marks oval patch of rudimentary elastic lamina. L = lumen. B, endothelial junction; arrow marks luminal end of cleft. The junction might be open, but slight darkening near arrow probably indicates gap type. Fine tubules next to abluminal end are probably associated with a patch of elastic lamina. (A × 28 700; B × 62 200.)

number of very small vessels immediately under the perineurium. These were usually obliquely sectioned, which may be explained by Lundborg's portrayal of many of the endoneurial vessels as helices (*in vivo* observations in the rabbit, 1970, 1979).

DISCUSSION

Identification of Capillaries

In size and structure the majority of the small vessels in the rat sciatic nerve closely resemble postcapillary venules, and Waksman (1961) concluded that the guinea pig had a large number of small venules instead of a normal capillary bed. There are, however, at least three reasons why these small vessels should not be designated postcapillary venules. (1) Since they are, with the exception of a few fine vessels, the smallest present, there is no evidence that any one of them follows an appreciable length of 'true' capillary. (2) Postcapillary venules in conventional vascular beds are

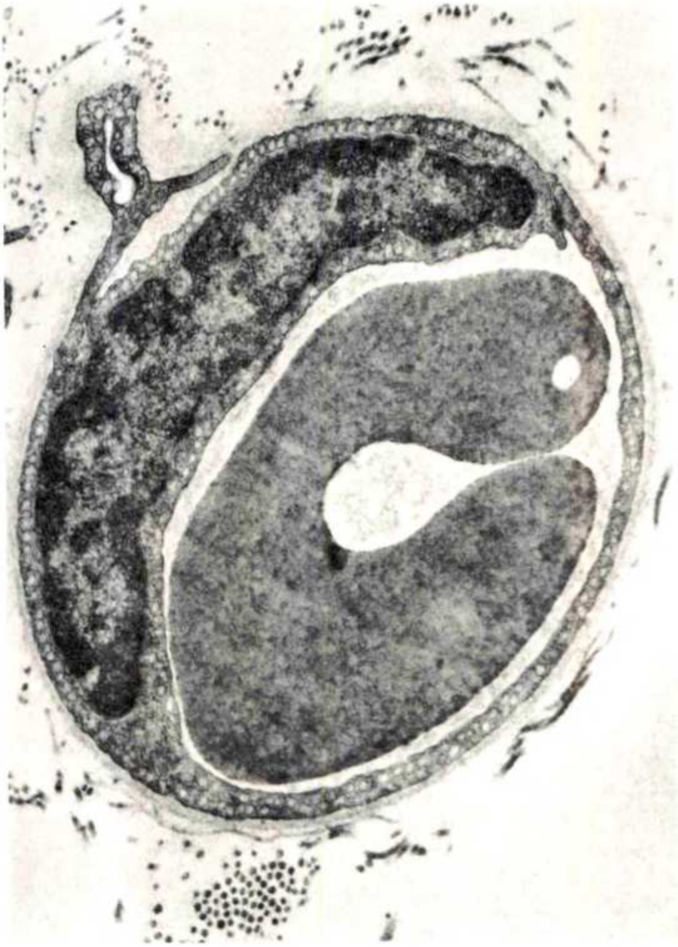

FIG. 13. Electron micrograph of a 'typical' capillary in rat skeletal muscle: smaller than an erythrocyte, with only one endothelial junction, it has little or no wrapping of periendothelial cells. (× 23 250.)

more permeable to certain substances and more susceptible to injury and vasoactive agents (like histamine, serotonin and prostaglandins) than the preceding capillaries (Arfors *et al.*, 1979); the presence of these characteristics, which may not be shared by the small vessels in the nerves, should not be implied by adopting the name associated with them. (3) Conventional postcapillary venules do not stain for alkaline phosphatase activity; the small vessels of the intrafascicular network, like a 'true' capillary bed, do. It seems reasonable to describe the finest mesh of the rat's sciatic microvasculature as a network of mainly large capillaries with an unusually complete investment of pericytes, and prominent, often complex, basal laminae. The guinea pig, cat and man have similar networks, the cat and man having a slightly higher proportion of small capillaries.

The rabbit intrafascicular vessels may constitute a special case, unusual, paradoxically, because their size is more 'typical'. In our quantitative study, they too

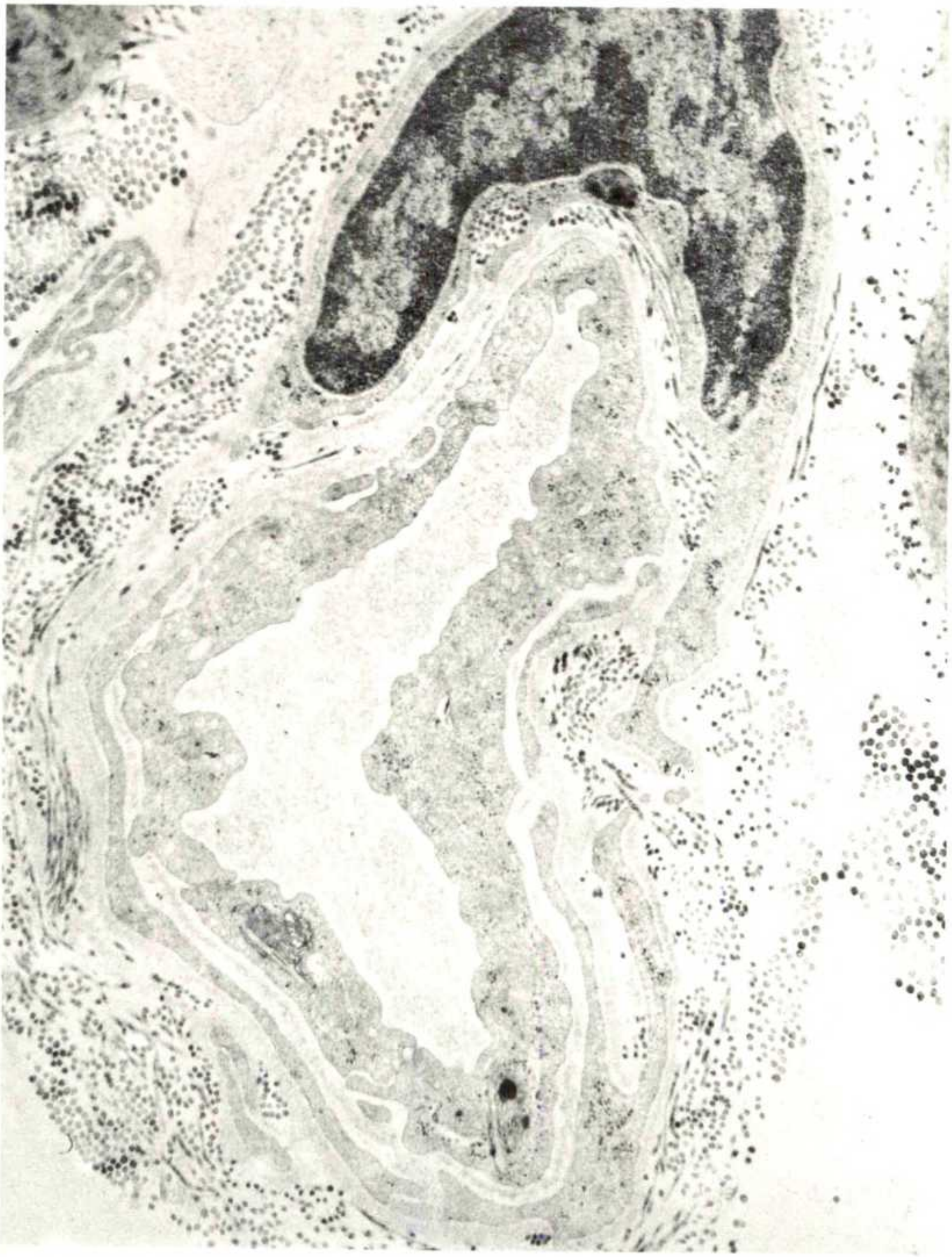

FIG. 14. Electron micrograph of one of the smallest vessels encountered in a (one year) rat nerve. At least three endothelial cells form its wall and it is nearly completely covered by a discontinuous periendothelial cell layer. While considered to be a capillary, it strongly resembles a postcapillary venule. (× 25 100.)

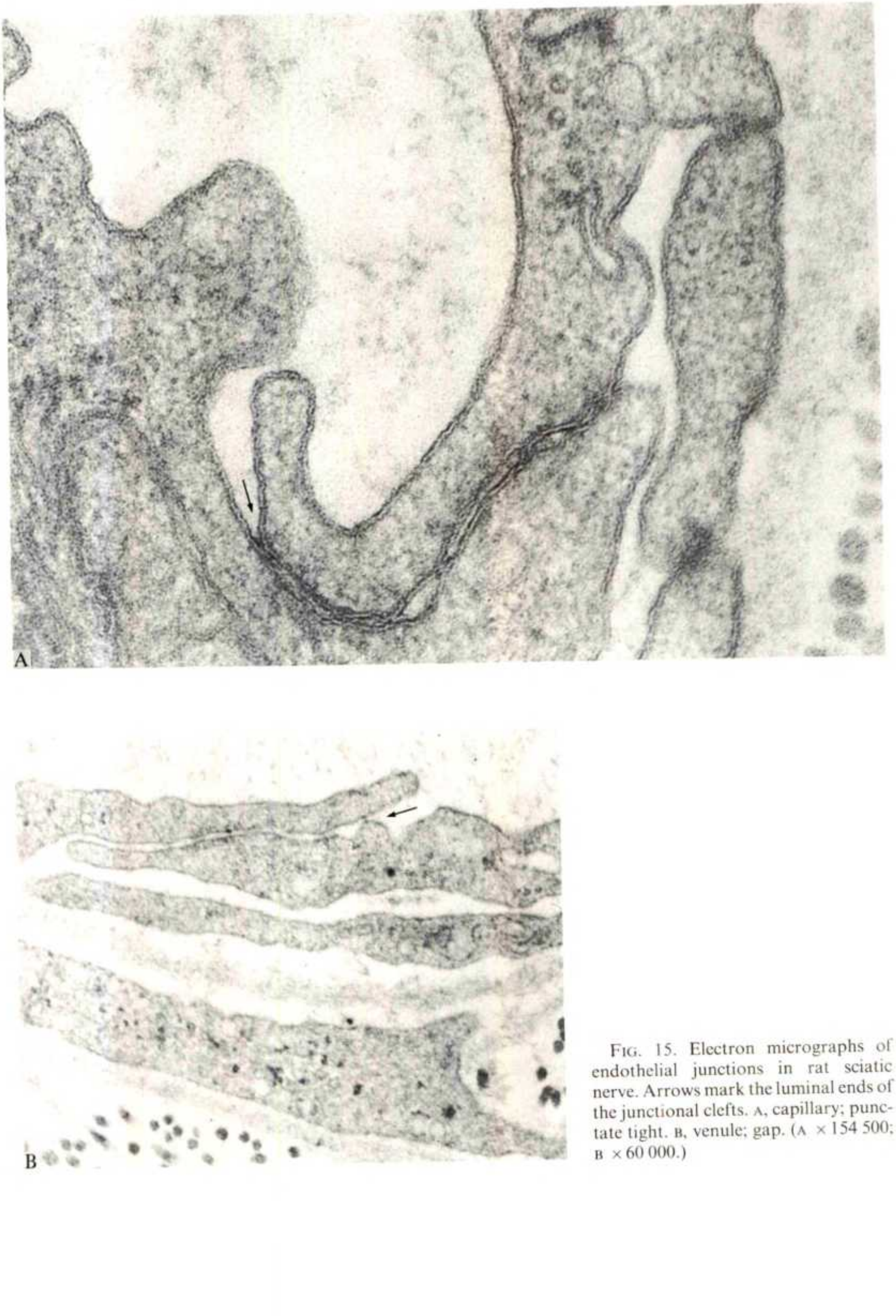

FIG. 15. Electron micrographs of endothelial junctions in rat sciatic nerve. Arrows mark the luminal ends of the junctional clefts. A, capillary; punctate tight. B, venule; gap. (A × 154 500; B × 60 000.)

often ran too obliquely to qualify for diameter analysis, and they were eliminated from the present alkaline phosphatase descriptive analysis by their lack of staining reaction. Waksman (1961) believed them to be small capillaries, and our deductions from other measureable parameters suggested the same conclusion (Bell and Weddell, 1984). Investigators such as Roberts *et al.* (1950) and Lundborg (1970), who performed detailed *in vivo* vascular studies on intraneural nerves, might have noticed departures from 'normal' size and spacing as obvious as those in the rat. They were, however, working on rabbits, and made no comment on these features. Until the present study, Waksman's comments on the guinea pig may be the only reported recognition of unusual vascular sizes and distributions within nerves.

Significance of Alkaline Phosphatase Activity

Romanul and Bannister (1962), who demonstrated the distribution of alkaline phosphatase in brain and muscle vasculatures, had no precise explanation for its presence there. They and others (Moynahan *et al.*, 1972) postulated a role in phosphate reactions for energy production to support transport or carrier mechanisms, a reasonable justification for distribution along the walls of a vascular tree. Interesting problems are then raised by species and organ variations, in particular the complete lack of activity in the vessels of the rabbit nervous system. An association has been postulated between strong alkaline phosphatase activity and either the absence of a barrier or the increase of its transmitting function (Pearse, 1958; Hennig, 1972; Suzuki, 1981). On the other hand, capillaries in the rat brain, peripheral nerves, skeletal muscles and ganglia, which represent the full spectrum of barrier function, all stain with comparable activity; any relationship that may exist between barrier and enzyme is not simple.

The electron microscopic localization of alkaline phosphatase activity in the pinocytotic vesicles of endothelium (Davies and Garrett, 1973) supports the idea that the enzyme is associated with transport of substances, if not across endothelial cells, at least into or out of them. Romanul and Bannister suggest that the cuff of staining activity in the initial segment of small arterioles might indicate a rapid sampling of blood chemistry by the endothelium, which then transmits some message to the muscle cells surrounding it. A sampling of extracellular fluid outside the arteriole might also be postulated. Local controlling mechanisms of this sort would seem appropriate in the intrafascicular compartment of the nerve, where fluctuations in regional ionic and osmotic balances must be rapidly and precisely amended, where blood flow directions are apparently altered with ease, and where direct innervation of arterioles is rare or absent.

Structural Aspects of the Blood-nerve Barrier

The vascular barrier in the nerve is not identical to that in the brain; it is more variable from one species to another and more susceptible to alteration by various chemical and pathological influences (Olsson, 1975). The range of interendothelial junction types observed here in the rat nerve may suggest one basis for functional variability; junctions in brain vessels are consistently tight. It is possible that the nature of some endothelial attachments is dynamic, varying with time and local conditions. Vessels in this study were fixed by immersion, whereas the electron microscopic observations of many other investigators were made on perfused material. It has been shown, however, that appearances of endothelial junctions in nerve and brain tissues do not depend on the method of fixation (Brightman and Reese, 1969; Olsson and Reese, 1971).

Pinocytotic transport across endothelial cells is minimal where vascular barriers exist, and brain endothelium shows very few vesicles. Numerous vesicles appear in vascular endothelium in nerve, but their function may be absorption of nutrients or chemical messages for the use of the endothelial cells themselves rather than transendothelial transport (Olsson, 1975).

In man and in the mouse, a breakdown in the blood-nerve barrier associated with leprosy infection was attributed to the appearance of endothelial fenestrations and discontinuities (Boddingius *et al.*, 1972; Boddingius, 1976). Such breaks in endothelial integrity were not seen here in the normal rat nerve.

A Unique Vascular Bed: Functional Implications

It is clear from microradiographs, alkaline phosphatase preparations and semithin and ultrathin sections that the vessels of the rat nerve are larger and more widely spaced than those of skeletal muscle. Vascular channels run for great distances along the nerve in the epineurium and endoneurium. Anastomoses are common between arterioles, between venules, and between arterioles and venules. The difficulty of obtaining a well differentiated arterial and venous injection, or occasionally of obtaining a good perfusion of fixative, has emphasized these interconnections. Because the smallest vessels are larger than ordinary capillaries, it might be said that the whole vascular bed of the nerve is a continuous anastomotic network. Lundborg (1970, 1975) described complex flow patterns through this network (even in the rabbit, where the vessels may not be as large as in some other animals): different flow directions were encountered simultaneously at different points along a given vessel as a result of anastomotic links, and the direction of flow was also seen to reverse in response to trauma or sympathetic stimulation.

This adaptable circulation, highly competent even under adverse circumstances, is more important for the balanced ionic and osmotic milieu of the endoneurial compartment in which the nerve fibres function than to the metabolic nourishment of the fibres themselves. It may act as an *in situ* reservoir; the relatively constant volume of blood, moving through large conduits, can be quickly rerouted. The ambiguous alkaline phosphatase pattern of the venous portion of the network, the large size and unusually complete pericyte reinforcement of the capillaries, and the varied interendothelial junction types may all be associated with variable flow directions and exchange functions.

Concurrent quantitative results (Bell and Weddell, 1984) showed that while the nerve has as large a vascular volume as the adjacent (white) muscle, it has a smaller number of larger capillaries and consequently a lower overall surface area for exchange; the metabolic demands on the blood may be less in the nerve. Zweifach (1939) stated that tissues requiring a relatively constant total blood flow, like nerve, have a large number of thoroughfare channels (interconnecting vessels larger than capillaries), whereas a tissue undergoing wide fluctuations of activity and metabolic demand, like muscle, tend to have conventional capillary beds fed by end arteries. The principle fits this context.

The thin walls and rudimentary elastic laminae of the arterioles may be associated with some unusual blood pressure effect produced by a distal vascular bed having less resistance than conventional small capillaries provide. Tissue pressure fluctuations in the endoneurium, restricted by the firm perineurium, are probably not as great as those in extraneural tissues, and the delicacy of the arterioles may also be a reflection of this reduced demand for reaction to external pressure changes. On the other hand, if intrafascicular tissue pressure does rise (e.g. in oedema), these arterioles might be particularly liable to collapse. Sjöstrand *et al.* (1977) postulated intrafascicular ischaemia under these conditions. Since the endoneurial compartment is effectively a closed one, transmission of changing pressure effects over some distance might occur, resulting in remote arterial reactions.

The leprosy bacillus is the only bacterial organism known to settle in nerve tissues, and it is probably carried there by the blood vessels (Rees and Weddell, 1970; Weddell *et al.*, 1971; Boddingius, 1977). It takes months longer to settle in nerve than in muscle tissue, perhaps because rapid transmission through large channels and flow reversals discourage contact with the endothelium. Altered flow patterns with slow or stagnant areas, perhaps caused by adjacent lesions, might provide the opportunity for the eventual invasion of endothelium.

Blood volumes of nerve and muscle tissue may be comparable; the distribution of that blood volume in the two tissues is, however, very different.

ACKNOWLEDGEMENTS

Research costs have been partially covered by a grant from Lepra. We are grateful to those who have assisted this work by providing working space and facilities, technical advice, cooperation with injection experiments, microradiographic consultation and assistance, help with photography and drawing, and review of manuscript, discussion and typing. We wish to thank, in Oxford: Professor Charles Phillips, Professor R. L. Saunders, Mr R. V. Ely, Messrs C., J., and A. Vereker, Dr W. Kanan, Ann Stanmore, Patricia Van Diest, Brian Archer, Jacquie Brazier, Sheona Couper and Christine Court. In London, Canada: the Departments of Pathology and Clinical Neurological Sciences, University of Western Ontario and University Hospital, Dr M. J. Ball, George Moogk, Mary Jo Stone, Judy Balint, Nancy Joslin, Kathy Stuart and Steve Mesjarik. Helpful questions and suggestions have also been received from Dr D. Oppenheimer (Oxford) and Professor P. K. Thomas (London, England).

At the time of submission M.A.B. was a research fellow of the Gerontology Research Council of Ontario at the University of Western Ontario.

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(*Received April 28, 1983. Revised January 19, 1984*)

Brain (1984), **107**, 899–920

THE CONTROL OF HAND MOVEMENTS IN A CASE OF HEMIANAESTHESIA FOLLOWING A PARIETAL LESION

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SUMMARY

A 46-year-old patient with a lesion limited to the left retrorolandic area without involvement of the prerolandic motor strip was examined. Anaesthesia to tactile, warm, cold, and painful stimuli was complete for the right hand and wrist. Position sense was abolished for the right wrist and finger joints. Performance of the right hand in motor tasks was severely impaired. Simple visual and auditory reaction times were lengthened. Sustaining a constant level of force was impossible. In the absence of visual feedback, only simple, monoarticular movements could be correctly executed; more complex movements requiring coordination between several joints, such as prehension, were poorly, or not, performed. The role of somatosensory cortex in conveying kinaesthetic input to the motor areas and the importance of vision in substituting for kinaesthetic loss, are discussed.

INTRODUCTION

Sensory information as to the position and motion of a limb has long been considered to exert a critical role in the initiation and execution of purposive movements with that limb. The classical claim was that this somaesthetic information, particularly that representing 'muscle sense', would generate at the cortical level an image of the limb to be moved, which, when activated, would be used for production of movement. This theory had received its main support from Mott and Sherrington (1895) who, in their experiments with monkeys, demonstrated the effects of complete deafferentation of one upper limb produced by section of the corresponding dorsal roots. Following operation, the animals were unable to perform purposeful movements correctly with their deafferented limb, particularly when the task involved the most distal segments (e.g. prehension). These awkward movements were, in fact, observed only when the animals were forced to use their deafferented limb, since in the free situation this limb remained virtually unused. This deficit was observed for up to eighteen months in one animal. Similar results were later obtained, also in monkeys, by Lassek (1953) and Twitchell (1954).

Sherrington's theory was questioned by Lashley (1917) who reported a patient with a deafferented leg following a gunshot injury of the spinal cord. This patient had been found to be able to perform, in the absence of visual control, active flexion-extension movements at the knee with reasonable control of amplitude and velocity. In later papers Lashley proposed that motor patterns should be considered as independent of sensory control for initiation and timing of muscle contraction, as well as for the intensity and duration of these contractions. He concluded that effector mechanisms were entirely preset at the central level because he believed that tactile, kinaesthetic and visual inputs triggered by a movement had latencies too long to account for feedback regulation (*see* Lashley, 1951). The present view as to the role of proprioceptive afference in motor control is certainly closer to Lashley's theory than that of Sherrington. It is currently claimed that both the initiation and execution of purposive movements can be observed in deafferented animals, that is, movements based exclusively on central motor programs. The only restriction is that animals must be allowed sufficient postoperative time to learn how to use their deafferented limb. In that event, precise movements, even those involving the fingers, can be performed surprisingly well (Bossom, 1974; Taub *et al.*, 1975; Gilman *et al.*, 1976).

In the present paper, we report a study of hand movements in a patient with a cortical lesion located in the left parietal lobe. Although this patient had no deafferentation in the usual sense (i.e. of peripheral origin) she was virtually unable to experience any sensation from her right hand and forearm. Clinical and radiological investigations suggested that the lesion was limited to the rolandic somatosensory strip and to the superior parietal lobule, and that the motor and premotor areas were intact. This rare occurrence provided a rather unique opportunity to test voluntary movements executed in the absence of somaesthetic control of cortical origin. The effects on movements produced by this cortical lesion were compared with those that follow more peripheral lesions of the somaesthetic pathway (Rothwell *et al.*, 1982). Finally, the possible role of visual feedback in substituting for the absent somatosensory information was examined.

CASE REPORT

The patient, R.S., is a 48-year-old right-handed woman who suffered several episodes of meningeal haemorrhage from a left occipital dural angioma. In September 1976, embolization treatment had been undertaken with the aim of occluding the occipital artery, the main afferent to the angioma. Pieces of gelfoam were introduced successfully into the angioma *via* the external carotid artery. When the catheter was pulled back, however, a fragment of gelfoam was unfortunately liberated into the internal carotid artery, which occluded a parietal branch of the sylvian artery. This produced infarction of a large zone in the parietal lobe of the left hemisphere. The postoperative arteriogram showed complete occlusion of the posterior parietal branch (which was intact on preoperative arteriography). The artery to the angular gyrus was also blocked but appeared to be filled retrogradely through a cortical anastomosis. A CT scan with high accuracy scanning (EMI 4400) revealed a clear-cut area of hypodensity which involved the whole postcentral gyrus (except for its mesial part), and the anterior part of the supramarginal gyrus. The precentral gyrus was apparently spared (fig. 1). The thalamus seemed to be intact although the thalamic parietal radiations were likely to be destroyed.

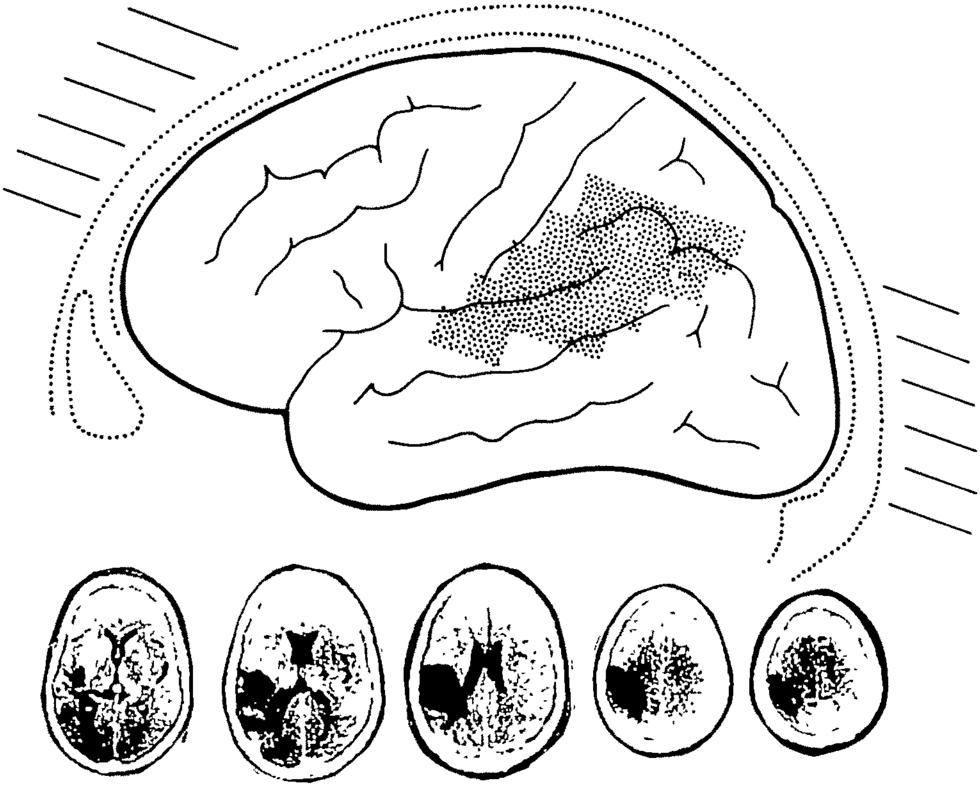

FIG. 1 Reconstruction of the lesion of R.S. The extent of the destroyed area on 5 CT scan sections has been outlined on a lateral view of the left hemisphere. (There is no section available above the fifth slice.)

Following this cerebral insult, R.S. presented a complex syndrome with a complete right homonymous hemianopia, right hemianaesthesia, and a right-sided hearing impairment (as assessed by complete right ear extinction in the dichotic listening test and absence of auditory evoked response over the left hemisphere, Michel and Péronnet, 1982). Aphasia was present with alexia and agraphia. Ideational apraxia was also observed but cleared rapidly. The linguistic deficit is currently very discrete: a few phonemic paraphasias and some elements of acalculia and agraphia. Right-left orientation is poor but no worse than it was before, according to the patient. No signs of posterior parietal involvement, such as unilateral visual neglect or optic ataxia, were present at any stage. The 'body image' was never perturbed.

RESULTS

Present Clinical Status

Visual fields. The visual fields were mapped using a Tubingen Perimeter (Dr M. T. Perenin). Dynamic perimetry with a large test stimulus (116 min of arc) showed normal visual fields (fig. 2, striped area). When a small test stimulus (10 min of arc)

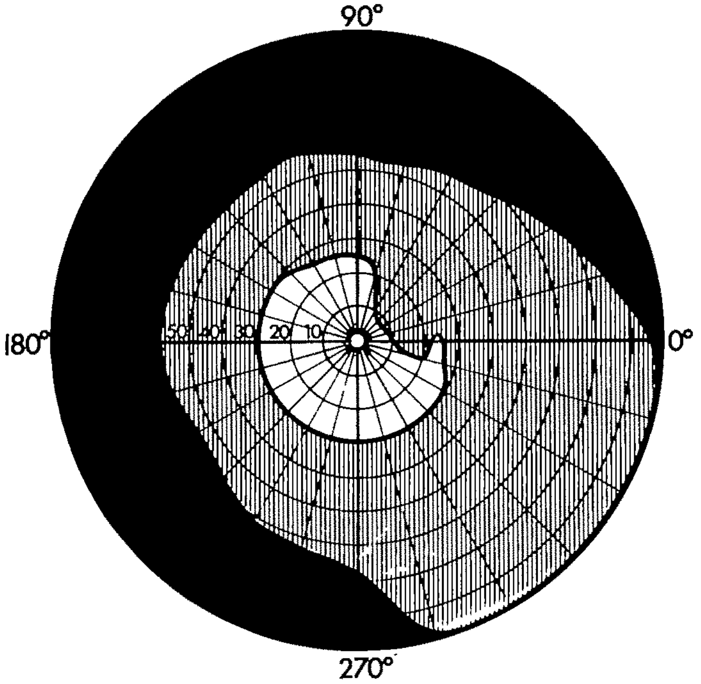

FIG. 2. Map of the visual field of the right eye, obtained with two different test stimuli. Striped area = extent of the visual field when using a large test stimulus (116 min of arc); white area = extent of the visual field when using a small test stimulus (10 min of arc within an area of 30 deg from the centre of the field). Note the right upper quadrantanopia with small stimulus only

was used to map the central 30 deg, a clear deficit appeared in the upper part of the right visual field beyond 10 deg of eccentricity (fig. 2, white area). This deficit was confirmed by static perimetry along the horizontal meridian.

Somatosensory testing. The somatosensory deficit now appears to be stationary, since little or no change has been observed on repeated examination over the past three years. The sensory loss for touch involves the right hand and wrist, where it is virtually complete. At the level of the right arm and shoulder, tactile anaesthesia is less severe, since strong stimuli are detected and grossly localized. The right half-face and the lower limb are also involved (fig. 3). Sensitivity to cold, warm and painful stimuli, as well as vibration, is impaired with the same distribution as the tactile deficit. It was noticed, however, that even in the area of most profound anaesthesia (i.e. in the hand), R.S. can localize tactile events when forced to point to the stimulated zone with her normal hand, even though she does not experience any sensation from that zone. This interesting finding has been reported in detail in a separate paper (Paillard *et al.*, 1983; *see also* Kohn and Dennis, 1974). It is reminiscent of the so-called 'blindsight' which has been described in the visual modality in patients with lesions involving the visual cortex (*see* Perenin and Jeannerod, 1978).

The recording of somatosensory evoked potentials proved to be of particular interest. After stimulation of the second and third digits of the right hand, the early parietal (postcentral) response (N2O-P27-P45 components) were absent. Despite this, a large precentral response (P22-N30) was recorded from frontal leads, suggesting the existence of a short latency pathway conveying somatosensory input to the prerolandic cortex (*see* Mauguière *et al.*, 1983, pp. 283–284).

Sensations evoked by passive movements are abolished at the fingers and wrist. At the right elbow, the direction of passively induced movements cannot be consistently detected. In the absense of visual control R.S. makes frequent errors whenever she indicates the direction of passive movements verbally or she tries to match the angle of her right elbow with her other arm. The level of detection is influenced by the velocity of the movement. A better detection is achieved when the movements are applied briskly, whereas slow movements are never detected.

At the right shoulder, the direction of passive movements can be detected with less error and matching with the other arm is reasonably good.

Assessment of motor function. Repeated neurological examination has never revealed any clinically detectable motor deficit. The tendon reflexes were found to be symmetrical in both the arms and legs. The plantar reflexes were flexor on both sides. Muscle tone in the right upper limb was normal.

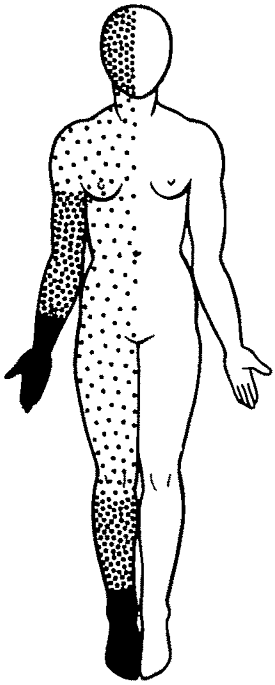

FIG. 3. Map of the somatosensory deficit. Black areas = complete anaesthesia, dotted area = relative anaesthesia. A higher density of dots indicates a deeper anaesthesia.

In the early stages of recovery, R.S. would not use her right hand spontaneously unless forced to; later, she spontaneously used her hand in everyday life for many types of actions, provided she could control her movements visually. She could reach for and manipulate objects, eat normally using a fork or a spoon, and write (though with difficulty). Without visual control, however, movements with her right upper limb became awkward and inefficient. This fact was particularly clear in

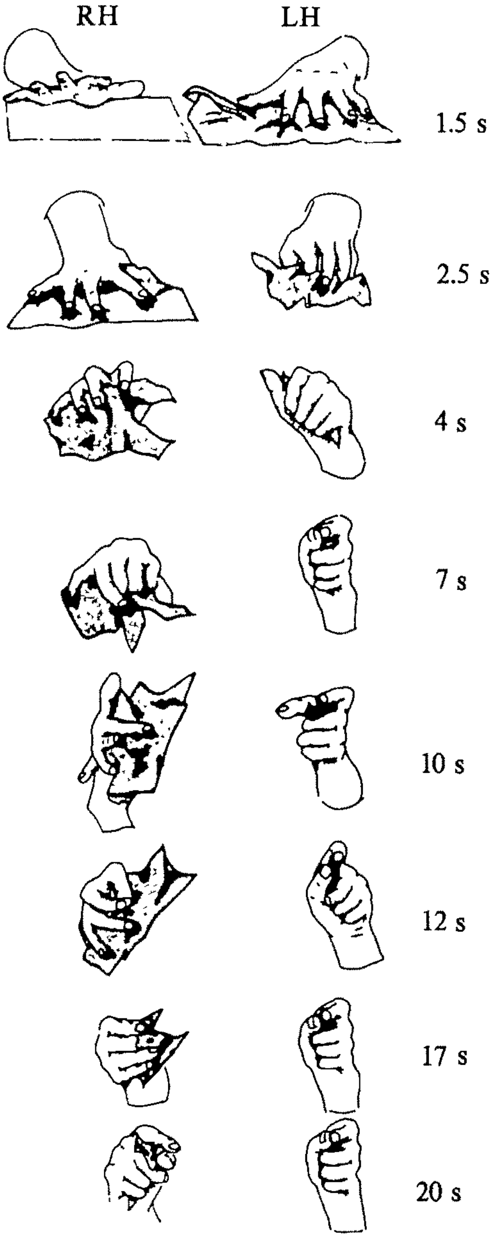

FIG. 4. Inaccurate finger movements of the right hand during crumpling a sheet of paper The two hands (RH, LH) have been redrawn from single frames of a film taken at 25 frames/s. Numbers on the right indicate the time (in seconds) from the onset of the movements

actions such as combing her hair or searching for objects out of sight. Similarly, R.S. had to watch her right foot when ascending stairs or stepping up the kerb of a pavement.

Independent and rapid finger movements, such as in drumming or tapping, were performed more proficiently under visual control. Tapping rate was about 4/s with the right index finger, as compared with 5/s with the left. This pattern of asymmetry was the reverse of what might be expected from a right-handed subject. In the absence of vision, the rate of tapping with the right index finger could not be sustained and rapidly degraded. However, R.S. could sustain an almost normal tapping rate when she could hear the taps.

Another simple test allowed us to compare independent finger movements performed with the right and the left hand. R.S. was required to crumple a sheet of paper simultaneously with each hand in front of a camera. She was allowed to watch her hands. Fig. 4 shows an example (redrawn from a film) where the task was achieved by the left hand in about 7 s, although it took more than 20 s to attain the same result with the right hand. Note also that the onset of the movements with the right hand was delayed with respect to the left.

Finally, R.S. was tested for her ability to make distal sequential gestures under visual control and without vision. Under visual control she was able to touch accurately with the tip of her thumb any part of the palmar surface of her four other fingers. Without vision, however, she was unable to do so. During her attempts, movements were clumsy and spatially disorientated. This observation is contradictory to that made by Volpe *et al.* (1979) in their patients with severe hemianaesthesia. Similarly our patient was found to be able to draw in the air figures or letters without difficulty under visual control. Without vision the same movements could not be executed. In her attempts, R.S. described verbally what she thought she was doing but her fingers appeared to move randomly and with a very limited amplitude. Looking at the videotape recording of these gestures an observer without knowledge of the underlying sensory deficit would probably term the impairment a ‘melokinetic’ apraxia.

Simple reaction time was studied by monitoring the depression of a key with either index finger in response to an acoustic or visual stimulus. In both conditions, reaction time was longer when the right index was used. The mean difference between right and left index finger reaction times was 35 ms in responding to the visual stimulus ($t = 2.21$, $P < 0.025$), and 130 ms in responding to the acoustic stimulus. In the acoustic condition, reaction time with either index finger was about 30 to 40 ms longer when the subject’s eyes were closed (Table 1).

TABLE 1 MEAN REACTION TIME (IN MS) AND SD FOR FINGER MOVEMENTS IN RESPONSE TO A VISUAL OR AN AUDITORY STIMULUS

	Left hand	*Right hand*
Visual stimulus	332 ms (51)	367 ms (49)
Auditory stimulus with vision	223.5 ms (52)	353.8 ms (81)
Auditory stimulus without vision	251.9 ms (36)	393.5 ms (96)

The ability of R.S. to apply a given level of force by sustaining an isometric muscle contraction was tested by getting her to track a target on a screen by pressing a strain gauge held in either hand. The force exerted on the strain gauge was recorded and also fed to the screen as a function of time. Consequently, the task consisted in matching the position of the target line with the force line. Fig. 5 shows sample records where the target line is a stationary (fig. 5A) or an oscillating line (fig. 5B). When the left (normal) hand was used, the target line was reached rapidly by increasing muscular contraction isometrically. The level of muscle contraction was then maintained with a high degree of precision whatever the required level of force. Closing the eyes did not affect the performance during the first 15 to 20 s. Later, the force exerted began to decline slowly and regularly. Reopening the eyes, however, produced an immediate readjustment of the force level (fig. 5A, upper row).

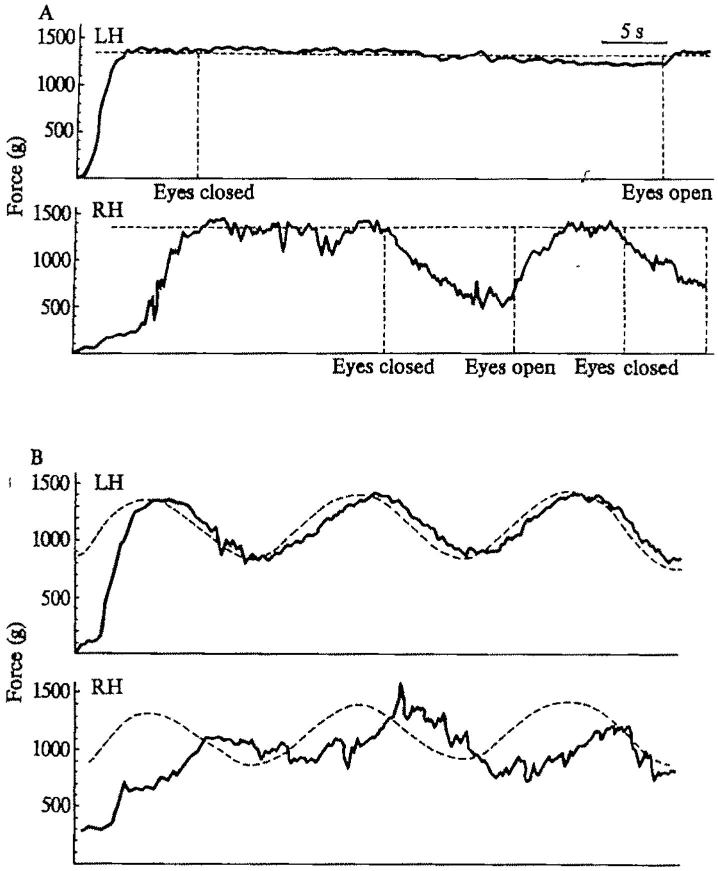

FIG. 5. Ability to match a visual target by changing the pressure exerted on a strain gauge. The heavy line indicates the record of force exerted by the left hand (LH) or the right hand (RH) in grams. A, the horizontal dotted line represents the position of a stationary visual target set at 1300 g. Notice difference in performance between the two hands, particularly when the subject closed her eyes; B, the dotted line represents a visual target oscillating between 800 and 1300 g.

When she used her right hand, it took R.S. more than 10 s to reach the target line. This slow increase in isometric contraction was produced in a stepwise fashion and the proper amount of force was maintained with difficulty. For a high level of required force (e.g. 1300 g), she made large oscillations around the required level (fig. 5A, lower row). For lower levels of force (e.g. 300 g), she usually overshot and maintained an exaggerated muscle contraction without being able to decrease it down to the required level.

When R.S. closed her eyes after she had approximately reached the target line she could not maintain muscle contraction and force diminished rapidly. When she reopened her eyes force was increased slowly up to the target level (fig. 5A, lower row).

Tracking an oscillating line by changing isometrically the degree of muscular contraction was easily achieved with the left hand. Fig. 5B (upper row) shows a very precise matching of the target line by the force line, with a phase lag of about 0.5 s. With the right hand, this task was found to be virtually impossible (fig. 5B, lower row).

Pointing Movements Directed at Visual Targets

Methods. Small light targets (light-emitting diodes) were presented on a horizontal plane at 60 cm from the subject's plane of gaze. One target was positioned on the subject's sagittal axis and will be referred to as the midline target. Other targets were presented at positions corresponding to 10, 20 and 30 deg from the midline target on one side (the side ipsilateral to the recorded hand) and to 10 and 20 deg on the other (the side contralateral to the recorded hand). The head rested on a forehead support.

The plane on which the targets appeared was a digitizing tablet recording the XY position of the subject's index finger when it was in contact with the tablet (Prablanc and Jeannerod, 1973). The subject was instructed to point rapidly and accurately at the targets when they jumped from the midline to one of the peripheral positions. Targets were presented in a random sequence.

The pointing performance of each hand was studied separately in both right and left space, that is, right or left from the midline. In addition, several conditions of visual feedback from the moving limb were used: (1) complete visual feedback, with continuous vision of the limb and of the target; (2) no visual feedback, with continuous vision of the target but no vision of the limb at any time; and (3) initial visual feedback. In condition (3) the limb could be seen prior to the movement but not during the movement. This was achieved by turning the lights off by means of an electromagnetic shutter, when the index finger was raised from the tablet. The target remained visible throughout.

The experiments involved 6 blocks of trials (3 conditions of visual feedback × 2 hands). Each of the 5 targets was presented 10 times (50 trials per block). Data were processed by measuring the latency of the movement, its duration, and the absolute pointing error Values for targets located symmetrically on the right or the left of the midline (10 and 20 deg) were pooled. An analysis of variance was made with three main factors: Hand (H), right and left; Condition of visual feedback (VF), complete feedback, no feedback, initial feedback; Space (S), right and left.

Results. Latency. The latency of the movements with the right hand were systematically longer than those with the left (Table 2) with a mean difference of 75 ms ($F_H = 15.1$, $P < 0.005$). In addition, for both hands the latency of movements was longer by 124 ms on the average when the target appeared in right space ($F_S = 42.1$, $P < 0.001$). The different conditions of visual feedback did not significantly influence latency ($F_{VF} = 1.43$, n.s.).

Duration. Movements of the right hand had a longer duration on the average than those of the left ($F_H = 17.1, P < 0.001$), especially for the condition of complete visual feedback. In this condition the movements of the right hand were 120 ms longer than in the nonvisual feedback condition. The difference was only 20 ms (and in the reverse direction) for the left hand, as commonly observed in normal subjects (Prablanc *et al.*, 1979). The side where the targets appeared was without influence when the data were considered as a whole ($F_S = 1.2$). However, movements with the right hand were clearly of a longer duration in right space in the complete visual feedback condition than in any other condition (Table 2).

TABLE 2. MEAN LATENCY AND DURATION (IN MS) AND VARIABLE ERROR (IN CM) DURING POINTING AT VISUAL TARGETS WITH THE LEFT OR THE RIGHT HAND

		Left space			*Right space*		
Condition	*Hand*	*Latency*	*Duration*	*Error*	*Latency*	*Duration*	*Error*
No visual feedback	L	473	347	1.4	603	404	3.1
	R	578	399	1.8	673	375	3.9
Initial visual feedback	L	454	288	0.9	662	358	1.9
	R	536	385	1.7	584	338	1.5
Complete visual feedback	L	416	367	0.7	534	347	0.4
	R	534	473	0.5	684	541	0.4

Hand pointing errors. The most important factor for accuracy of pointing appeared to be visual feedback ($F_{VF} = 142.6, P < 0.001$). However, the effect of the lack of visual feedback on accuracy was slightly more marked for the right hand than for the left ($F_H = 4.4, P < 0.05$). Finally there was a marked effect of the side where the targets appeared, since errors were larger in right space for both hands ($F_S = 57.3, P < 0.001$), (Table 2, fig. 6).

Visually Directed Prehension

Methods. The subject sat in front of a box divided horizontally by a semireflecting mirror into two equal compartments. She looked through a window within the upper compartment, and placed her right or left arm below the mirror, that is, in the lower compartment. Small solid objects (e.g. a small sphere) were placed in the lower compartment in the subject's sagittal plane at 20 cm to 40 cm from the body. A cine camera running at 50 frames/s was placed on one side of the box in order to film the radial aspect of the hand under study. Three different conditions of visual feedback from the hand movements were used: (1) complete visual feedback in which the subject could see the lower compartment through the mirror; she had a continuous vision of her hand and the target prior to and during her movements; (2) terminal visual feedback, in which vision of the hand was masked before the onset and during the early part of the movement, but became available in its later part; and (3) no visual feedback, in which the view of the hand was masked throughout the movement, although the target remained visible permanently. This was obtained by inserting a mask below the mirror between the two compartments. Thus the subject could see in the mirror the virtual image of an object placed at the top of the upper compartment and projecting in the lower compartment. This protocol is commonly used in eye-hand coordination experiments (Held and Gottlieb, 1958).

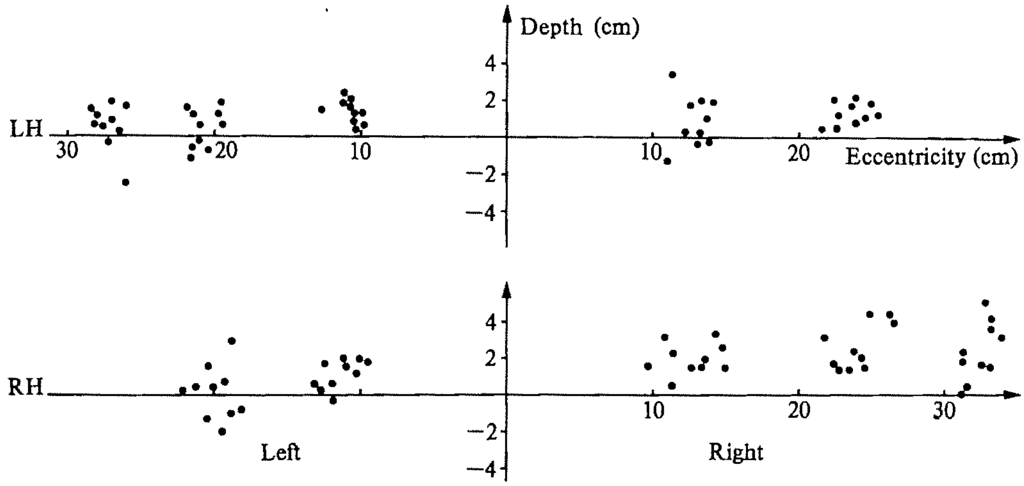

FIG. 6 Two-dimensional scatter of hand pointings directed at visual targets appearing in the left or right hemispace. Upper row = left hand (LH) pointings; lower row = right hand (RH) pointings

The subject was instructed to place the hand under study on a starting block, with the forearm in the prone position and the fingers semiflexed. She was required to reach and grasp the target object as fast and as precisely as possible and to carry it near the starting block. No formal time constraint was given. Prehension movements were analysed separately for each hand. Only a few trials were made for the left (normal) hand. For the right hand, two distinct sessions were made, where trials in each of the three visual feedback conditions were alternated. A total of 50 trials was obtained for that hand. Data were processed by projecting frame by frame the image of the movement on a screen, with a one-to-one magnification. Duration of the movement was measured as the number of frames between the first detectable arm displacement and contact with the target-object. The position of anatomical details of the wrist was plotted over successive frames. Distance between successive positions gave an approximation of the instantaneous tangential velocity for the arm trajectory. From the same frames, the respective postures of the fingers could be studied qualitatively, and reproduced by outlining the image of the hand on the screen.

Results. Reconstruction of the movement from the film frames reveals two segmental components during prehension. One component involves transportation of the hand as a whole at the vicinity of the target (transportation component). The other involves a posturing of the fingers in anticipation to contact with the target-object (manipulation component) (Jeannerod, 1981).

With her normal (left) arm, R.S. behaved like a normal subject. In the no visual feedback condition (i.e. the most restrictive condition), movements performed with that arm were fast and accurate. Average total movement duration was 552 ms (SD 39.1).

The trajectory of the transportation component of the left hand had the usual bell-shaped profile (fig. 7A). The hand was first raised from the table and

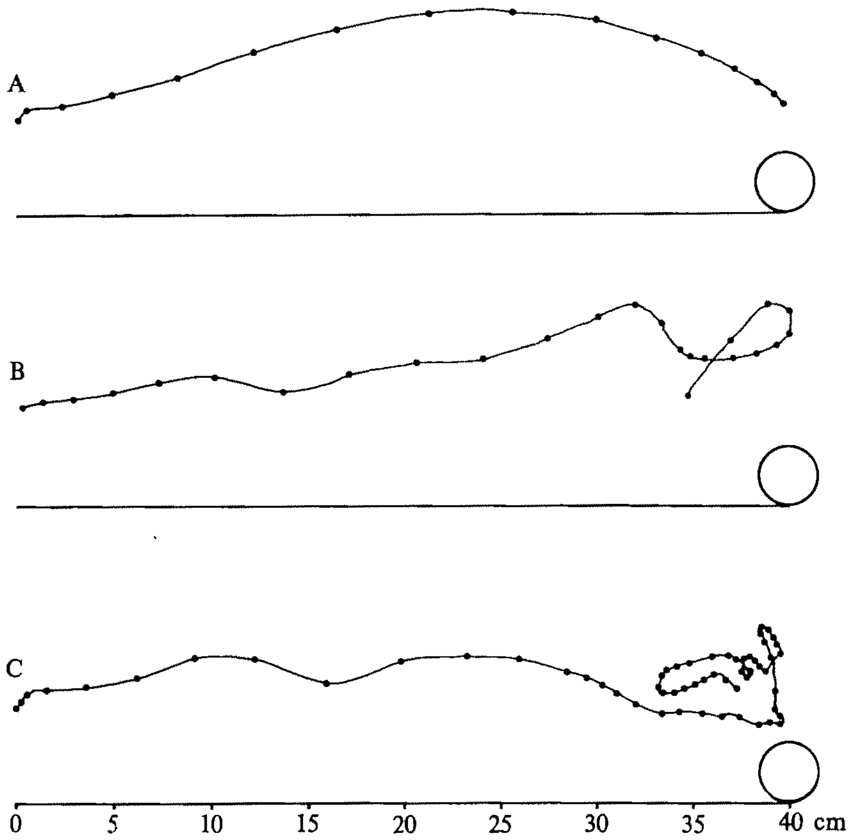

FIG. 7. Trajectory of the arm during reaching movements directed at a spherical object located 40 cm in front of the subject. Each dot on the graphs represents the position of the wrist on successive film frames. Time interval between 2 dots = 40 ms. A, reaching movement of the normal left arm in the no visual feedback condition; B, reaching movement of the impaired right arm in the terminal visual feedback condition; C, reaching movement of the impaired right arm in the no visual feedback condition.

subsequently lowered down to the object at the same time as it was moved in the direction of target location. Analysis of the velocity profile of this transportation component allowed us to differentiate between an initial phase of the movement, where tangential velocity reached its peak, and a final low velocity phase. In the no visual feedback condition, the peak of tangential velocity had a mean of 90 $cm \cdot s^{-1}$ (SD 12.2). It was reached on average after 272 ms (SD 29.9). The low velocity phase was of short duration, not exceeding one fourth of total movement duration, as usually observed in normal subjects (fig. 8, upper left) (Jeannerod, 1981).

The manipulation component was marked by an early posturing of the fingers, as in the example shown in fig. 9A. This posturing typically involves first an extension and subsequently a flexion of the fingers in anticipation of the grasp. It has been shown in normal subjects that the fingers begin to close in the last one fourth of movement duration, namely at the time of the low velocity phase of transportation (Jeannerod, 1981).

Prehension movements performed with the arm contralateral to the lesion were in no way similar to those performed with the normal arm. In all conditions, the shape of the trajectory of the transportation component was different from that of the normal hand. The right hand was usually swept towards the target, sometimes without losing contact with the table. Under those circumstances, the hand was raised at a later stage when near the object. This is illustrated in the lower two rows of fig. 7 (B and C). However, the quality of execution of prehension movements by the right hand was closely dependent upon the availability of visual feedback from the moving hand.

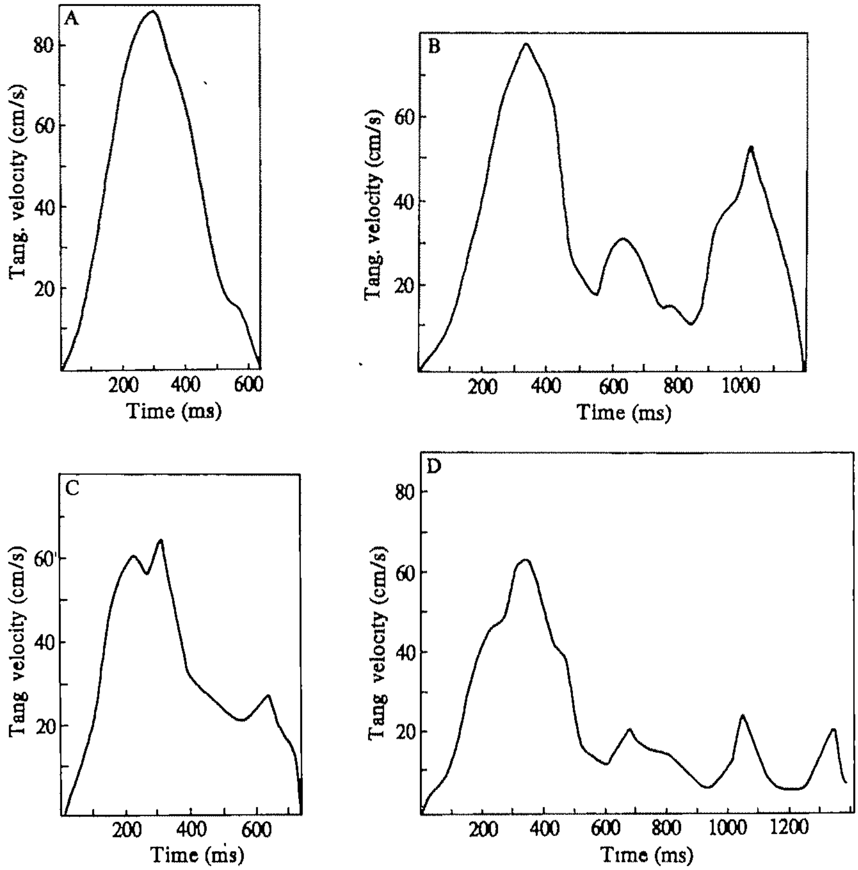

FIG. 8. Velocity profiles of movements of the left and right arms during prehension for different visual feedback conditions. Tangential velocity is obtained by plotting the position of the wrist every 40 ms and measuring the distance between successive points. The curves have been smoothed manually A, movement of the left arm in the no visual feedback condition; B, movement of the right arm in the terminal visual feedback condition; *lower row*; movements of the right arm (C) in the complete visual feedback condition and (D) in the no visual feedback condition

In the complete visual feedback condition (i.e. vision of the hand available throughout) mean total movement duration was 813.3 ms (SD 162.7) and thus much longer than with the normal hand. This increase in movement time was not due to a slowing in the early phase of the transportation component, since the peak of tangential velocity was reached, on average, after 226.6 ms (SD 18.8). Peak velocity was 74.8 cm·s^{-1} (SD 12.4). Inspection of the velocity profile of these movements revealed that the increase in movement time was due to the contribution of the low

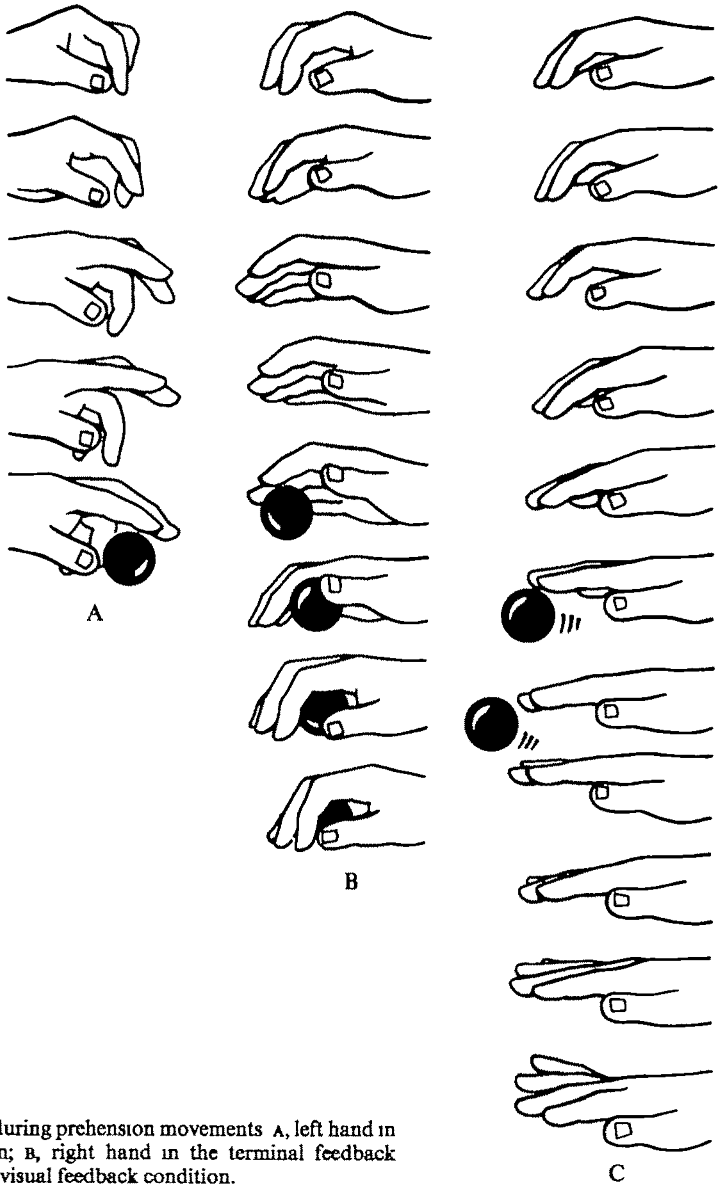

FIG. 9. Posturing of the fingers during prehension movements A, left hand in the no visual feedback condition; B, right hand in the terminal feedback condition; C, right hand in the no visual feedback condition.

velocity phase of the trajectory (fig. 8, lower left). This was confirmed in conditions where visual feedback was either just in the initial phase or absent. In these conditions, the initial phase of transportation was only slightly modified with respect to the complete visual feedback condition, so that peak velocity was reached after about 260 ms on average (248 ms, SD 100.8 in the initial visual feedback condition; 296 ms, SD 74.1 in the no visual feedback condition). Peak velocity, however, was rather low (64.8 cm·s^{-1}, SD 11.6 and 63.6 cm·s^{-1}, SD 14, respectively.

By contrast, the late phase of transportation was severely affected by deprivation of visual feedback. In the no visual feedback condition, the low velocity plateau had a virtually infinite duration: the hand kept endlessly 'searching' above the object location without making the final grasp (fig. 8, upper right). Obviously in such cases, movement duration could not be measured. In the terminal visual feedback condition, the peak of tangential velocity was followed by a long lasting, low velocity plateau until a second high velocity peak occurred. As a consequence, the movement ended with a brisk grasping of the object (fig. 8, lower right). It seems that, in the absence of visual feedback, the low velocity phase cannot be ended and no grasp occurs (*see below*); when visual feedback becomes available again, a new ballistic movement with a high velocity peak is generated and eventually yields to grasping of the object. Total movement duration in this situation was 1032 ms (SD 226).

The manipulation component of prehension movements was found to be severely impaired in all conditions tested. Basically, the anticipatory finger posturing, so clearly observed in movements with the normal hand, was lacking. Extension of the fingers could be seen after the onset of the movement and the hand was kept outstretched without anticipatory flexion of the fingers. In the no visual feedback condition, the fingers remained spread out during 'searching' for the object. After some time finger extension tended to become exaggerated and this posture was maintained until the end of the trial (fig. 9C).

In the complete and terminal feedback conditions, some late and incomplete posturing was observed. This resulted in awkward prehension in which the whole palmar surface of the hand was involved in the grasp, rather than fingertips only (fig. 9B). A confirmatory (though more anecdotal) finding seems worth reporting. In a few additional trials, the subject's right hand was placed at the starting position in an inadequate posture (fig. 10). This posture, unnoticed by the patient, was maintained until it was revealed by direct visual inspection. Then it took several hundreds of milliseconds to restore the correct posture for prehension.

Finally, in one series of trials the right hand, instead of being placed on the table at the starting point, was placed in contact with another part of the body. Several locations were attempted, such as the forehead, the chest, or the left hand. In the latter instance, the left hand was placed on the table with the right resting on it. These procedures invariably improved the execution of prehension movements by the right hand. For instance, when the left hand was used as a starting support, in the complete visual feedback condition, movement duration was 490 ms on average (SD 53.8); the time to velocity peak was 170 ms (SD 22.3) and peak velocity 86 cm·s^{-1}

(SD 11.7). These values are in the same range as those obtained for the left hand. The manipulation component was also improved, but to a lesser extent.

The clear improvement in the time course of prehension, however, was associated with difficulties in initiating the movement. Indeed, when R.S. had to start a movement with her hand touching another part of her body, she had to make a visible effort to release her hand from this active posture, as if it were 'glued' to the body.

DISCUSSION

It is obviously difficult in such a clinical case, despite the good resolution of the available CT scan images, to localize the cortical lesion of the left hemisphere in terms of cytoarchitectonic areas. Nevertheless, a few reasonable assumptions can be made. First, although the thalamus appears to be intact, a substantial proportion of its corticopetal fibres in the posterior part of the corona radiata are probably severed. In addition to this massive cortical deafferentation, the CT scan clearly shows a large lesion of the postcentral gyrus, corresponding to the parietal somatosensory strip (Kaas *et al.*, 1981). Thus SI (areas 3, 1 and 2) is likely to be destroyed, as also is SII, since the lesion includes the parietal operculum. In the posterior part of the parietal lobe, the lesion additionally involves area 5 and a large part of area 40 but apparently spares area 7. Finally, the lesion apparently does not extend frontally beyond the rolandic sulcus, thus leaving intact areas 4 and 6 and the supplementary motor area. This lesion therefore represents the rare occurrence of a complete destruction of the somaesthetic area without the usual involvement of the motor area.

The topography of the right hemianaesthesia, which was complete for the distal segments of the upper limb and incomplete for its proximal segments, as is commonly found in hemianaesthesia of parietal origin (Foerster, 1916; Critchley, 1953), might suggest that the upper part of the left postcentral gyrus in which elbow and shoulder are represented, had been spared. This is probably not the case. Even though direct visualization of this area was not obtained with the CT scan, it has to be assumed that it was involved in the infarction because it belongs to the same vascular territory as the other parts of the gyrus. Obstruction of the parietal branch of the left sylvian artery was clearly apparent on the arteriogram. Although the mesial part of the somatosensory cortex seemed intact on the CT scan, it was probably deafferented by the lesion of the thalamic radiations.

Preservation of sensation from the right arm and shoulder is more likely to represent the contribution of ipsilateral somatosensory pathways. In monkeys, uncrossed pathways have been shown to reach the secondary somatosensory area *via* an extralemniscal route (Mehler *et al.*, 1960). Accordingly, unilateral parietal ablation in this animal produces a measurable ipsilateral sensory loss (Semmes and Mishkin, 1965) in addition to the classical contralateral deficit. In man, the existence of an ipsilateral somatosensory cortical representation is attested by clinical observations in hemidecorticate patients. Such patients can report sensation when the arm contralateral to the cortical ablation is stimulated, although with a higher threshold and a poorer spatial discrimination (Kohn and Dennis, 1974). These stimulus characteristics were also observed in our patient for the sensations elicited at the level of her right shoulder. Alternatively, this residual sensation, together with the ability of R.S. being able roughly to localize stimuli on her right arm without identifying them (a tactile analogue of 'blindsight'), might be related to the persistence of noncortical somaesthetic afferents to the cortex, especially direct thalamic fibres reaching the motor cortex from the oral part of the ventropostero-lateral nucleus (Asanuma *et al.*, 1979*a*, *b*, in cat; Lemon and van der Burg, 1979, in monkey). These afferents, however, if present, apparently did not give rise to subjective experience.

Apart from this direct thalamic input, the motor cortex and motor supplementary area in cats and monkeys receive most of their direct cutaneous and kinaesthetic input from the somatosensory area (Jones and Powell, 1970). Particularly in the monkey, area 3a is known to receive low threshold muscle afferents. From there, movement-related information could reach the motor cortex, hence representing the ascending limb of a transcortical sensorimotor control loop (Wiesendanger and Miles, 1982). Provided this organization also holds for man, destruction of the somatosensory area, including area 3a, thus implies that the motor cortical area is deprived of its main normal proprioceptive input. It is conceivable, however, that such a corticocortical deafferentation will not affect to the same extent the distal and the proximal segments of the upper limb. Distal segments, which are almost exclusively controlled by the crossed corticospinal tract, should be more affected than the proximal segments which seem to be controlled by both motor cortices (Brinkman and Kuypers, 1973). In other words, for the proximal segments, ipsilateral somatosensory afferents could represent the anatomical substrate of a transcortical loop within the right hemisphere, or alternatively within the left hemisphere after a callosal transfer. This difference in sensorimotor organization for distal and proximal segments could explain the different levels of performance of R.S., whether she used her hand or her shoulder. Although her finger movements apparently lacked any proprioceptive control, shoulder movements could benefit from such control *via* ipsilateral pathways and therefore be more accurately performed. Pointing at targets located at arm length, a movement effected mostly at the shoulder level was found to be performed with reasonably good accuracy.

Clinically, this loss of cutaneous and proprioceptive control at cortical level produced major impairments in the execution of distal voluntary movements. First, movement initiation seemed to be delayed. This fact was apparent in our patient not only in the reaction time studies (responses with the right forefinger could be delayed by up to 130 ms with respect to the left), but also in many other motor tasks (e.g. the paper 'crumpling' test, pointing at targets, etc.). To explain this slowness, it might be suggested that somatosensory afferents at the level of the motor cortex normally play the role of maintaining a state of excitability which will necessarily decrease as a consequence of deafferentation. This suggestion is merely a revised version of the classical Sherringtonian theory (*see* Introduction), and corresponds to the so-called 'afferent paresis' described by Foerster (1936). According to Luria (1973) afferent paresis is a situation created, among other causes, by a lesion of postcentral cortical zones, in which 'the potential strength of the muscles remains intact, but differential control over the limb is sharply reduced so that the patient cannot perform voluntary movements with his hand . . . which has lost its kinaesthetic sensation' (Luria, 1973, p. 170).

R.S., however, could still initiate simple movements of her right hand or fingers when her eyes were closed, that is, in the complete absence of conscious sensory information from the segments to be moved. This remaining capacity is not a particular feature of this patient, due for instance to the persisting direct thalamic input to her motor cortex. Even complete somaesthetic deafferentation does not prevent initiation of simple motor patterns. This has been shown by Rothwell *et al.* (1982) in a patient presenting complete anaesthesia of two hands from a peripheral neuropathy. Both their patient and R.S. could easily perform simple monoarticular movements, such as raising one finger or tapping, without visual control. More complex tasks involving coordination between fingers (touching the fingers with the thumb, drawing in the air, grasping and manipulating objects) could not be executed by R.S. in the absence of vision. This fact was particularly apparent during prehension movements where grasping and manipulation of the object could not be achieved with the right hand. Paradoxically, the patient of Rothwell *et al.* was better than R.S. at such tasks although, as stated by the authors, his performance would degrade rapidly if the same movements were repeated several times. A similar observation was made by Bizzi and Polit (1979) and Polit and Bizzi (1979) in monkeys with one deafferented arm. These animals have been shown to match correctly the position of visual targets by monoarticular flexion-extension movements of the forearm. However, if the task was made more complex by changing the initial position of the arm, the monkey failed completely.

The fact cannot be neglected that the lesion, in addition to deafferenting the motor and premotor areas from strictly sensory inputs, might also have disconnected those areas from more integrated inputs, coming from the posterior parietal areas. In fact, R.S.'s difficulty in performing complex motor tasks with the deafferented limb was not due to impairment at the 'conceptual' level of motor control: she knew what to do when asked to perform a movement. In addition the quick disappearance of the initial ideational apraxia seems to rule out such a 'disconnection' hypothesis. Failure of her overt movement was more likely to be due to a difficulty in selecting the proper pattern of innervation when a high degree of coordination between segments was required. This impairment may have resulted in an exaggerated degree of cocontraction of the agonist and antagonist muscles of the involved segments. Cocontraction seems to be a common finding in such patients (Rothwell *et al.*, 1982) and has been documented by EMG (*see* Luria, 1973, fig. 44). Its detrimental effect obviously will be more apparent in complex movements where the timing of activation of the different segments becomes critical. In this patient, however, no EMG study has been performed. Clinically, cocontraction might be an explanation for the difficulty shown by R.S. in initiating a prehension movement when she was involved in an active posture with her arm (such as touching her forehead or chest), when she had to shift from one agonist-antagonist innervation pattern to another.

Finally, the other major impairment shown by R.S. was her inability to maintain a given level of muscle contraction with her deafferented hand. Although she could produce and sustain (though with difficulty) the required level of force with the help of vision, she was no longer able to do so with the eyes closed, when the level of force rapidly declined. This finding, which was also reported by Rothwell *et al.* in their patient, seems to reflect the main effect of deafferentation on motor control, namely, the inability to follow up an action once it has been initiated. It could be suggested that the motor cortex, although it can initiate motor patterns without information as to the actual status of peripheral effectors, would need reafference from these effectors in order to produce the next pattern in the sequence. In other words, cutaneous and proprioceptive information gained during active movements would be essential for the sequential timing of an action when it involves muscular contractions at more than a single joint (*see also* Roland, 1978). Persistence of somatosensory afferents at the spinal and cerebellar levels, and at the level of other subcortical structures, did not provide sufficient cues for maintaining a correct movement control. R.S.'s performances with her affected hand were virtually similar to those of other patients presenting deafferentation of a more peripheral origin. It therefore seems that deafferentation of motor cortex is the critical factor in impairment of motor control produced by deafferentation at any level of the somatosensory pathways.

Clinical cases like the present one offer the unique opportunity for studying the substitutive role of other sensory modalities, especially vision, when somaesthetic control is lacking. R.S. behaved with her right hand in a strikingly different way depending upon whether she was able to guide her movements visually. Without vision, actions involving the fingers could not be sustained, and initiation was difficult if not impossible. A good example is given by the task of touching various areas on the palmar surface of the hand with the thumb: as soon as R.S. was prevented from watching her hand, the movement became slow and erratic. Another example comes from the study of prehension. The reaching phase of the movement was correctly executed, although the grasping phase was misadapted due to the inability to shape the hand according to the spatial configuration of the object. Finally, during manipulation, or in other actions which necessitate active touch, such as palpating objects or crumpling a piece of paper, visual guidance was only of little help.

Clearly visual feedback alone cannot completely substitute for somatosensory information. Besides, a serious limitation for the use of visual information in movement control is the long duration of the visuomotor loop. A typical (and perhaps optimistic) estimate for this delay is around 130 ms (Carlton, 1981). In some studies, delays as long as 250 ms have been measured (Keele and Posner, 1968) that is, a value much longer than that for the somatosensory loop (around 90 ms, according to Marsden *et al.*, 1978). Results obtained from our experiments with R.S. have revealed even longer delays. In the study of prehension, it sometimes took up to 500 ms to initiate the final phase of the movement after sight of the hand had been restored.

In experiments with normal subjects the inappropriateness of vision for controlling an ongoing movement *via* a feedback loop can only be suspected. It is only in a very limited number of clinical cases, such as the present one, that this insufficiency can be directly demonstrated.

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(*Received September 20, 1983. Revised January 26, 1984*)

Brain (1984), **107**, 921–933

LESION SIZE AND LOCATION IN IDEOMOTOR APRAXIA

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SUMMARY

Lesion size correlated positively with the severity of apraxia in the acute (one month) and chronic (one year) stage in 177 stroke patients, but accounted for only 25 per cent of the variance of the apraxia scores. Apraxia was measured on a standardized battery and defined in relation to normal controls. Lesions visualized by CT were traced objectively and measured on standard templates. Small lesions (less than one-tenth of the hemispheric volume) producing moderate or severe apraxia were mostly frontal and close to the body of the lateral ventricle. The lesions of the deep parieto- and occipitofrontal and anterior callosal fibres seem to be crucial in apraxia, rather than the parietal cortex as traditionally claimed. Large lesions (more than three-tenths of the hemisphere) without apraxia were associated with atypical asymmetries in half of the cases, as measured by the torque and the width of the frontal and occipital lobes on CT scan, suggesting a right hemisphere role in sparing and recovery of praxis.

INTRODUCTION

Since the introduction of the term apraxia by Steinthal (1871), several studies have addressed the question of the anatomical basis of apraxic disorders. Most of them have relied on the study of single cases or a small number of necropsy studies of apraxic patients, while others that have collected data from a larger series have only approximate localization. Before the introduction of computerized tomography the localization of lesions in these series was usually defined at the hemispheric (left-right), quadrantic (pre-postrolandic) or lobe level. Different aetiologies and length of disease were considered together, limiting the validity of generalization from the localization findings. The prevailing anatomical and behavioural model of ideomotor apraxia was established by Liepmann (1905) and further developed by others (Geschwind, 1965). Briefly this model states that auditory and visual information concerning the gesture to be made or imitated evokes its spatial kinaesthetic motor pattern in the left multimodal parietal lobe. The selected pattern is then transferred to the left premotor and motor area *via* ipsilateral parietofrontal connections located in the superior longitudinal fasciculus. In the frontal lobe further sequential elaboration may take place. If the gesture is performed with the left hand the program is transferred to the right premotor and motor areas *via* the anterior half of the corpus callosum. This associationist schema had been challenged by several authors who claimed that apraxia was due to diaschisis (von Monakow, 1914), mass effect (Lashley, 1929) or loss of abstract attitude (Goldstein, 1948) and could not be related to specific areas. Indeed, although most of von Monakow's (1914) apraxic patients had left parietal lesions, so did some of his nonapraxic subjects. The few systematic clinicoradiological studies of apraxia lesions located by CT scan produced contradictory results concerning the existence of lesion sites which regularly produce apraxia. While Tognola and Vignolo (1980) identified the frontal and central opercula and anterior insula as crucial areas for the imitation of oral gestures, Basso *et al.* (1980) could not find any difference in lesion sites between patients with and without ideomotor apraxia except for a higher frequency of deep lesions in the nonapraxics. In the present study we investigate the relation between lesion size, location and apraxia in order to identify the crucial areas in the left hemisphere where damage disrupts praxis and to analyse some cases of large left hemisphere lesions in which apraxia was absent.

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METHOD

Subjects

Two hundred and ninety-five correlations between lesions seen in CT scans and apraxia were studied in 177 adult right-handed native English-speaking patients who had sustained a single ischaemic stroke of the left hemisphere; 109 were male and 68 female. Their ages ranged from 27 to 85 years (mean 62.9, SD ± 12.8); 152 were examined in the first month of their illness (acute group), 143 at three or more months postonset (chronic group) and 118 patients during both the acute and chronic stages. The relationship of aphasia and apraxia in this group was explored in another study. Twenty-one age-matched nonbrain-damaged controls were also examined on all the tests.

Procedure

All patients completed a comprehensive neuropsychological evaluation comprising the Western Aphasia Battery (WAB) (Kertesz, 1982), which included language, reading, writing and apraxia subtests, drawing, calculation, block design and Raven's Coloured Progressive Matrices. The patients were classified with respect to their aphasia according to previously published numerical criteria (Kertesz, 1979). The acute group consisted of 9 nonaphasic, 34 global, 30 Broca's, 4 transcortical motor, 1 mixed transcortical (isolation of speech area syndrome), 21 Wernicke's, 8 conduction, 5 transcortical sensory and 40 anomic patients. The chronic group included 18 global, 33 Broca's, 5 transcortical motor, 6 Wernicke's, 1 transcortical sensory, 7 conduction and 56 anomic patients.

Apraxia Test

The apraxia test consists of 20 items in four descriptive categories. The items marked with an asterisk provide a test for object use.

Facial. (1) Put out your tongue. (2) Close your eyes. (3) Whistle. (4) Sniff a flower*. (5) Blow out a match*.

Intransitive (*upper limb*). (1) Make a fist. (2) Salute. (3) Wave goodbye. (4) Scratch your head. (5) Snap your fingers.

Transitive (*instrumental*). (1) Use a comb*. (2) Use a toothbrush*. (3) Use a spoon to eat*. (4) Use a hammer*. (5) Use a key*.

Complex. (1) Pretend to drive a car. (2) Pretend to knock at the door. (3) Pretend to fold a paper*. (4) Pretend to light a cigarette. (5) Pretend to play the piano.

The patient is asked to carry out each movement on verbal command first. If no response or an incorrect response is given, the patient is then shown the movement by the examiner and he is encouraged, verbally and gesturally, to imitate it. In order to eliminate comprehension difficulty, we deviated from the usual scoring method of the WAB which gives less credit for performance on imitation than on command. If good performance was achieved by either method, the patient received a score of 3. Impaired, but recognizable performance was scored 2, and poor, only approximate performance scored 1. If the patient performed with an object only, a credit of 1 was given. No performance, unrecognizable or unrelated gesturing, or erroneous use of objects were scored 0. Maximum score for all items was 60. Although this is a clinical and therefore subjective rating scale, there is a high reliability ($r = 0.99$) between examiners (Kertesz, 1979).

The cut-off score separating apraxics from nonapraxics was calculated based on the results of 21 nonbrain-damaged, age-matched hospital patients. The cut-off score for each movement category was the score immediately below mean -2 SD of control scores (Facial = 14; Intransitive = 12; Transitive = 12, Complex = 11.7). The cut-off score for the whole apraxia test (49.7 points) was then computed by adding these partial scores. None of the normals scored below this point.

Apraxic patients were divided into three categories of severe, moderate and mild impairment, according to their total apraxia score. Mild impairment was defined as a score ranging from the cut-off score to two-thirds of the cut-off score, moderate impairment as scores ranging from two-thirds to one-third of the cut-off score and severe impairment scores below one-third cut-off score.

CT Scan Measurements

All patients had a CT scan, in the acute, chronic or both periods. The lesions were traced on oblique templates by a radiologist who was not aware of the aphasia or apraxia scores. The templates were drawn from the atlases of Shipps *et al.* (1975) and Gonzalez *et al.* (1976). Matsui and Hirano's (1978) atlas was used to identify the anatomical structures involved in specific cases. Lesion size was measured by using a digitizer program to outline the tracings in each cut and adding the values to obtain a volumetric estimate of size. The methods are described in more detail in a previous publication (Kertesz *et al.*,1979).

The volume of the left hemisphere (ventricular system not included) was determined by summing the area of individual templates. Lesions were grouped into three categories according to their size, expressed as a ratio between lesion size and hemispheric volume. Lesions were considered small when their size was less than one-tenth, and large when they were greater than three-tenths of the volume of the hemisphere. Moderate sized lesions ranged between these two values (Tables 1 and 2).

An anatomical checklist was used to specify the anatomical sites involved in the cases discussed below. For each site, involvement was rated from 0 to 3 (0 = no involvement; 1 = less than 50 per cent; 2 = more than 50 per cent; 3 = complete involvement). The degree of cerebral atrophy was assessed by the ventrical: brain ratio, that is, the ratio of the width of frontal horns at the head of the right caudate nucleus and the width of the right hemisphere at the same level.

The pattern of skull asymmetry (torque and width of frontal and occipital lobes) that has been found to be related to cerebral dominance was determined for each case. Measurements were taken following the procedure described by LeMay (1977) at the level of CT cut that included the pineal.

RESULTS

Lesion Size and Apraxia

Tables 1 and 2 show the distribution of acute and chronic patients according to lesion size and apraxia scores. In both groups severity of apraxia and lesion size correlated positively (Pearson $r = 0.39$, $P < 0.05$ and $r = 0.5$, $P < 0.005$, in the acute and chronic groups, respectively). These values indicate that lesion size accounts for 25 per cent of the variance of apraxia. In 9 acute and 3 chronic patients small lesions were associated with moderate to severe apraxia, while 9 acute and 14 chronic patients had large left hemisphere lesions not associated with apraxia.

Small Lesions Producing Moderate to Severe Ideomotor Apraxia (Table 3)

With the exception of 2 cases (acute Cases 2 and 3), small lesions causing moderate to severe ideomotor apraxia had similar behavioural correlates and anatomical location. These patients were, in general, severe nonfluent aphasics with right hemiplegia, so they had to perform imitation of limb gestures with their left arm. Their lesions were subcortical, mostly in the frontal lobe. Involvement of basal ganglia was not a prominent finding. Instead the lesions appeared on the higher cuts, lateral to and in close relationship to the body of the lateral ventricles, involving the anterior half of the periventricular white matter. The tracings of these lesions by an independent radiologist are superimposed on fig. 1. Lesions in this location damage both longitudinal white matter tracts (superior occipitofrontal and superior longitudinal fasciculus) and the anterior callosal radiation, severing fibres joining homologous areas of the premotor and prefrontal areas.

Case 2 had an unusual localization. The CT scan disclosed a left inferior temporo-occipital and small splenial infarction caused by left posterior cerebral artery occlusion. This patient presented moderate Wernicke's aphasia, alexia with agraphia and bilateral ideomotor apraxia. Either the affected area was larger than that shown on the CT scan or the language and praxis 'areas' extended more posteriorly than usual. Imitation and recognition of gestures are not usually impaired in left posterior cerebral artery occlusions associated with pure alexia (Ferro *et al.*, 1982). Also, ideomotor apraxia is not a feature of surgical section of the

TABLE 1 LESION SIZE AND SEVERITY OF APRAXIA IN ACUTE PATIENTS

	Lesion size		
Lesion/hemisphere ratio	< 1/10	1/10–3/10	> 3/10
Volume of lesions	< 3.58	3.58–7.16	> 7.16
No apraxia ($\geqslant 50$)	44	15	9
Mild apraxia ($\geqslant 33 - < 50$)	14	7	6
Moderate apraxia ($\geqslant 17 - < 33$)	7	2	13
Severe apraxia ($\geqslant 17$)	2	9	20

$\chi^2 = 42.90$, df $= 6$, $P < 0.001$.

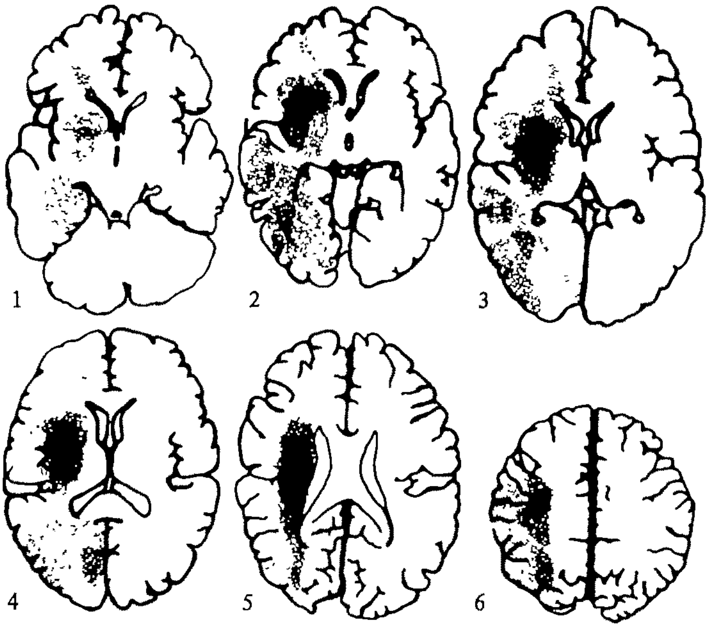

FIG 1 Superimposed CT scan abnormalities for 9 cases of small lesions and severe apraxia. The lower cuts have lower numbers.

TABLE 2 LESION SIZE AND SEVERITY OF APRAXIA IN CHRONIC PATIENTS

	Lesion size		
Lesion/hemisphere ratio	< 1/10	1/10–3/10	> 3/10
Volume of lesions	< 3.58	3.58–7.16	> 7.16
No apraxia ($\geqslant 50$)	48	24	14
Mild apraxia ($\geqslant 33 - < 50$)	10	4	16
Moderate apraxia ($\geqslant 17 - < 33$)	1	5	12
Severe apraxia (< 17)	1	2	6

$\chi^2 = 34.19$, df $= 6$, $P < 0.001$.

splenium (Trescher and Ford, 1937). Probably the left parietal lobe was disconnected from the visual associative areas by the combination of the left occipital and callosal lesions. This case may represent an unusual location of the inter- and intrahemispheric fibres carrying gesture-related visual information. In Case 3, with Wernicke's aphasia, a posterior infarct of moderate size was present, involving most of the supramarginal and angular gyri, mainly between posterior and middle cerebral artery territories.

Although in some of these cases, moderate corticosubcortical atrophy was present, none of the patients presented clinical or neuropsychological evidence of dementia. Skull vault asymmetries were measured but none of these patients had a complete 'left-handed' pattern, that is, larger left frontal and right occipital lobes.

TABLE 3 SMALL LESIONS CAUSING MODERATE/SEVERE APRAXIA

Age, sex	71 M	73 F	75 M	78 F	74 M	73 F	76 F	81 F	82 F
Hemiparesis	+	–	–	+	+	–	+	+	+
Type of aphasia	G	W	W	A	G	A	B	B	G
Apraxia score	26	30	27	32	11	33	26	26	13
Frontal white matter					1				
Premotor cortex					1				
Rolandic cortex						1			
Central white matter	1			1		2	1	1	2
Insula, external capsule				1		1			
Internal capsule, ant. limb							3		1
Internal capsule, post. limb									
Lenticular nucleus	1						2		3
Caudate nucleus	1						1		
Supramarginal gyrus			2						
Angular gyrus			2						
Parietal white matter	1		1		1				
Superior parietal lobe					2				
Superior temporal gyrus			1						
Middle temporal gyrus			2						
Inferior temporal gyrus		1							
Occipital lobe		2	1		1				
Ventricle/brain ratio	0.23	0.12	0.15	0.08	0.15	0.14	0.12	0.23	0.14
Skull asymmetries									
Frontal width	=	R	R	R	=	R	=	R	=
torque	R	R	R	=	=	R	R	=	=
Occipital width	L	L	=	=	L	=	L	=	=
torque	L	L	R	=	=	R	L	=	L

+ = present; – = absent, B = Broca's aphasia, C = conduction aphasia, A = anomic aphasia, G = global aphasia; W = Wernicke's aphasia; 1 = less than 50 per cent damaged, 2 = more than 50 per cent damaged, 3 = complete damage, R = right larger than left, L = left larger than right, = indicates same size

Large Left Hemispheric Lesions not Associated with Apraxia

Among patients with large left hemisphere lesions, 9 acute (18 per cent) and 14 (30 per cent) chronic patients (7 being follow-up of the acute cases) were not apraxic (16 total). In general, these patients had large frontocentral cortico-subcortical lesions. In some cases the inferior parietal lobe was significantly involved (5 acute and 6 chronic cases) and in 3 of these patients the lesion did not extend to the frontal lobe, although parietofrontal connections were always affected. All patients were right handed, but there was a remarkable incidence of an uncommon pattern of skull asymmetry among them. One patient had a typical left-handed pattern, left frontal and right parietal being wider (chronic Case 11). Four patients had larger right occipital torques and in 3 of them the right occipital lobe was also wider than the left. In 3 others the left frontal lobe had either a larger torque and width, or was wider than the right. This means that 50 per cent (8 out of 16) had partial or complete

TABLE 4. LARGE LEFT HEMISPHERE LESIONS WITHOUT APRAXIA ACUTELY

Age, sex	69 M	66 F	57 F	50 F	63 M	71 M	59 F	52 M	71 M
Hemiparesis	+	–	–	–	–	–	+	+	+
Type of aphasia	B	C	A	C	W	W	B	B	B
Apraxia score	58	56	56	60	53	59	50	60	56
Frontal white matter	2	1					2		
Premotor cortex	1	1		1			2		2
Rolandic cortex	2	2					3	2	3
Central white matter	2	2	1					2	2
Insula, external capsule	3	3		2			2	2	2
Internal capsule, ant. limb	2	1					2		3
Internal capsule, post. limb	3	1							2
Lenticular nucleus	3	2					2		2
Caudate nucleus	3	1					2		2
Supramarginal gyrus	2	3	1	1		1			1
Angular gyrus				2	2	2			
Parietal white matter	1	1		1	1	2			1
Superior parietal lobe	1								
Superior temporal gyrus	3	3	1	2	2	2	1		
Middle temporal gyrus			3	1	1	2			
Inferior temporal gyrus			1						
Occipital lobe			1						
Ventricle/brain ratio	0.15	0.12	0.12	0.07	0.07	0.07	0.12	0.08	0.11
Skull asymmetries									
Frontal width	R	R	R	R	R	L	L	R	R
torque	R	R	=	R	R	=	L	R	R
Occipital width	R	R	R	L	L	L	L	L	=
torque	=	R	R	L	L	L	L	L	=

Abbreviations as in Table 3.

reversal of the more common right-handed pattern of skull asymmetry, which usually consists of larger right frontal and left occipital lobes. These patients were also significantly younger than the apraxic subjects with small lesions (mean age 60.9 ± 8.0 *vs* 76.1 ± 4.5; t = 5.23, df 24, $P < 0.01$). They also showed less cerebral atrophy (mean ventricle/brain ratios 0.11 ± 0.03 *vs* 0.15 ± 0.05, t = 2.69, df 24, $P < 0.05$).

Table 4 provides data on the 9 patients who had relatively large lesions acutely but no significant apraxia. Three of these patients had reverse occipital, and 2 others reverse frontal asymmetry. Four of the lesions were predominantly posterior (temporal and/or angular gyri) in location. The chronic patients had even larger central and frontal lesions, but recovery probably played a more important role in the dissociation than lesion location or anatomical asymmetry.

DISCUSSION

The results of this study indicate that the severity of apraxia and lesion size are positively correlated and, in general, small left hemisphere lesions are not associated with a great deal of apraxia. Significant exceptions to this general rule are of especial interest. In fact 9 acute and 2 chronic patients presented moderate to severe ideomotor apraxia caused by relatively small lesions. Furthermore, 18 per cent of acute, and 30 per cent of chronic patients with large left hemisphere lesions did not show apraxia on imitation. This finding supports the view that apraxia is the result of localized left hemisphere lesions and not solely the total amount of left hemisphere damage. Indeed, lesion size *per se* explained only about 25 per cent of the variance in apraxia scores.

Basso *et al.* (1980) constructed composite histograms by which the antero-posterior distribution of all CT lesions were plotted. They failed to detect differences between the profiles for patients with and without ideomotor apraxia except for a higher frequency of deep lesions in the nonapraxic group. However, these authors recognized that their plotting technique could yield little information if the critical factor for producing apraxia was not so much the localization of the bulk of the lesions but that of a portion that they proposed might disrupt midcallosal fibres. The superimposition of all positive cases to contrast with the negative ones could be misleading for several reasons. (1) Vascular lesions producing ideomotor apraxia are not randomly distributed in space. They occur mainly in the middle cerebral artery distribution. Superimposing a large number of lesions would outline the middle cerebral territory, but may obscure anatomical-functional correlations. (2) Large lesions include both the areas that are responsible for apraxia and 'noise' areas whose damage does not produce any specific impairment in praxis, but can contribute to reduced performance by nonspecific effects (mass-effect, diaschisis). (3) Analysis of patients without apraxia could be important in order to separate the functionally crucial areas from 'noise' areas. Involvement of the critical areas should be minimal in each negative case. However, negative cases seek medical consultation and neuropsychological testing because they suffer from other left hemisphere disturbances, namely, right hemiparesis and aphasia. In general, these signs are also caused by middle cerebral artery infarcts. Superimposition of the lesions from a large number of negative cases will therefore be likely to produce a 'vascular' outline that is difficult to distinguish from the composite profile for positive cases. (4) Patients that, despite being right handed, have peculiar patterns of cerebral dominance and bihemispheric representation of praxis, would be included among nonapraxic cases. Their lesions would certainly increase the 'nonfunctional' areas, reducing the possibility of detecting praxis areas when comparing the composite profiles of positive and negative cases. This is clearly illustrated in the present series, as the nonapraxic/large lesion patients would be considered negative.

In the present series only some of the small lesions producing ideomotor apraxia involved the multimodal parietal lobe (angular gyrus and surrounding areas). This is in accordance with the findings of other researchers. Liepmann (1905), von Monakow (1914), Foix (1916), Nielsen (1946) and Ajuriaguerra *et al.* (1960) found lesions responsible for ideomotor apraxia located in the parietal lobe. However, Hécaen (1978) and Basso *et al.* (1980) argued against this location. Kolb and Milner (1981) found that the largest deficit in a task requiring imitation of complex movements of the arm occurred with lesions of the left parietal lobe. The angular gyrus is also important for the recognition of gestures (Ferro *et al.* 1982). Roland *et al.* (1980) found increased CBF over the parietal lobe in association with voluntary movements in extrapersonal space, and Heilman (1979) proposed that the visuokinaesthetic engrams of learned movements are localized in the dominant parietal lobe.

The most frequent location of small lesions producing apraxia was not the parietal lobe in our series but the anterior half of the periventricular white matter. These lesions damaged the frontoparietal connections, the occipitofrontal fasciculus and the anterior portion of the callosal fibres that connect the premotor areas. When the lesions were slightly larger and extended laterally, they also involved the superior longitudinal fasciculus, whose role on performing gestures under verbal command was emphasized by Geschwind (1965). In some cases the superior longitudinal fasciculus was certainly spared, while the occipitofrontal fasciculus was involved. In one case both pathways were spared but the extreme and external capsules were damaged along with the insula. Tognola and Vignolo (1980) showed that these pathways are important for the imitation of buccofacial movements, but in our patient arm movements were also impaired.

The periventricular lesions are in accordance with the Liepmann (1905) and Geschwind (1975) model for apraxia. Such lesions cause disconnection between the parietal and frontal lobes and prevent visuokinaesthetic motor patterns from the parietal lobe from contributing to the premotor cortex in programming correct movements. As these patients had right hemiplegia they often had to perform gestures with the left hand. Some subcortical lesions also interrupted interfrontal callosal connections contributing to left hand apraxia in patients whose dominant parietal lobe was intact. Otherwise these patients should be able to imitate gestures *via* an interparietal and right parietofrontal route. This would support Geschwind's (1965) proposal that left visuomotor connections are dominant for the imitation of movements.

The Liepmann-Geschwind model emphasizes the role of the arcuate fasciculus in connecting language association areas to the premotor area, in the performance of gestures on verbal request. However, the occipitofrontal fasciculus appears to be important for the imitation of movements. The same holds for the other extensive parietofrontal connections (Pandya and Kuypers, 1969; Jones and Powell, 1970) that were certainly damaged by the periventricular white matter lesions. Apraxia is considered to be a disorder of learned movements (Geschwind, 1975) and apraxic patients show impaired motor learning (Heilman *et al.*, 1975). Learning a new movement is much more dependent on establishing new visuomotor and somaesthetic motor associations than on verbal input. This may explain why damage to the occipitofrontal and parietofrontal pathways seems more crucial for producing ideomotor apraxia than an arcuate fasciculus lesion. Fig. 2 summarizes the converging pathways required to process practised movements. This system can be interrupted from lesions in various cortical regions, but subcortical convergence of the longitudinal motor associations in the left hemisphere seems to be most vulnerable.

In a number of patients, large left hemisphere lesions that included the parietal lobe and/or frontoparietal connections, failed to produce apraxia. Bihemispheric representation of function is a plausible explanation for this absence of apraxia. In those cases where the left multimodal parietal lobe was completely infarcted, it can be assumed that visuokinaesthetic motor organization is bilaterally represented and that the right visuomotor and somaesthetic motor connections were functionally active. This also means that in these patients gestures had been learned by both hemispheres, or that at least the right hemisphere was able to substitute easily and shortly after the left hemisphere insult. There is evidence from other studies to support this possibility. Indeed, some patients with callosal lesions can imitate

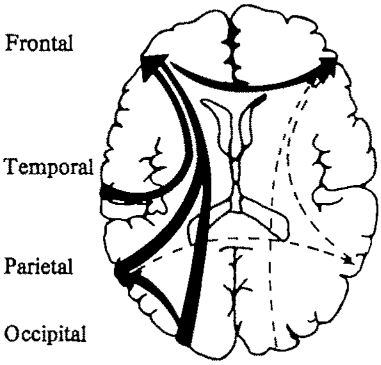

FIG. 2. Mechanisms of praxis. The longitudinal connections of the parietal, occipital and temporal regions to motor areas can be interrupted by a relatively small periventricular lesion in addition to widespread cortical damage. The compensatory pathways subserving recovery are shown with interrupted lines.

movements and use objects with both hands (Geschwind and Kaplan, 1962), and in other commissurotomized patients left hand apraxia recovers rapidly (Gazzaniga *et al.*, 1967). Furthermore, imitation of meaningless movements is often impaired following right hemisphere lesions (Kolb and Milner, 1981; De Renzi *et al.*, 1980). Although the left hemisphere is dominant for most motor tasks, especially those requiring motor sequencing (Kimura and Archibald, 1974), for other tasks such as copying static hand postures, both hemispheres appear equivalent while the right is superior in individual and paired finger flexion (Kimura and Vanderwolf, 1970). In addition, failure to use objects is more often the consequence of bilateral than of left hemisphere lesions (Hécaen, 1962) and some patients with extensive left hemisphere damage can recognize gestures (Ferro *et al.*, 1982). All these studies point out the bihemispheric contribution to motor skills.

Another source of evidence supporting the conclusion that the absence of apraxia following large left hemisphere lesions is due to bihemispheric representation of function, was provided by skull measurements obtained from CT scans of these patients. Fifty per cent of them, although being right handed, had unusual patterns of skull asymmetries, their left frontal lobes and/or their right occipital lobes having larger torques or width. However, these findings must be interpreted with caution as similar patterns were observed in two apraxic patients in this series with small left hemisphere lesions.

Nonapraxic patients with large left hemisphere lesions were younger and showed less cerebral atrophy on CT scans than apraxic patients with small lesions. Cerebral atrophy in the latter group, however, was not out of proportion for their age and they did not show clinical or neuropsychological signs of dementia. Although the possibility of the association of a critical vascular lesion with incipient Alzheimer's dementia can be raised, an alternative explanation is that in older patients the right hemisphere has a decreased ability to imitate gestures. This could be related to right visuomotor and somaesthetic motor connections being progressively less able to handle learned motor skills, because of lack of practice (given that left hemisphere areas dominate these activities). Alternatively the right hemisphere in older patients, having lost plasticity because of ageing, may no longer be able to learn new skills or to reactivate motor skills previously acquired through the left hemisphere.

ACKNOWLEDGEMENTS

This study was partly supported by an Ontario Ministry of Health Grant PR 696 to Dr Kertesz and by a fellowship from the Portuguese National Research Institute for Dr Ferro. Some of the data collection for this research was supported by a grant from the Ministry of Health of Ontario, project number DM 324, for a study of language therapy and recovery from aphasia to C. Shewan and A. Kertesz.

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(*Received July 27, 1983. Revised January 19, 1984*)

Brain (1984), **107**, 935–950

ENDONEURIAL BLOOD FLOW AND OXYGEN TENSION IN THE SCIATIC NERVES OF RATS WITH EXPERIMENTAL DIABETIC NEUROPATHY

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SUMMARY

Endoneurial hypoxia has been postulated to be important in the pathogenesis of diabetic peripheral neuropathy and may be due to reduced nerve blood flow. Neither blood flow nor oxygen tension have previously been measured in peripheral nerve in diabetic neuropathy. We have therefore measured both nerve blood flow and endoneurial oxygen tension in the sciatic nerves of 8 rats with streptozotocin-induced diabetes for four months, and in 8 age-matched controls. In 7 of the diabetic animals mean nerve blood flow was 8.7 ± 1.3 $\mathrm{ml \cdot min^{-1} \cdot 100\ g^{-1}}$ which is significantly less than mean nerve blood flow in the controls (13.08 ± 0.8 $\mathrm{ml \cdot min^{-1} \cdot 100\ g^{-1}}$; $P < 0.01$). In one diabetic animal, nerve blood flow was too low to be accurately measured. The reduction in nerve blood flow in diabetic neuropathy is due to an increase in resistance to flow which may be due to microangiopathy and to blood hyperviscosity. Endoneurial oxygen tension was also significantly reduced in experimental diabetic neuropathy in which 60 per cent of the oxygen measurements were less than 25 mmHg, compared with 19 per cent in the controls. Nerve blood flow was also measured in rats with experimental galactose neuropathy in which there is more marked sugar-alcohol accumulation, endoneurial oedema and elevation of endoneurial fluid pressure than in experimental diabetic neuropathy. The results obtained in this neuropathy suggest that the reduction in nerve blood flow which occurs in experimental diabetic neuropathy is due largely to factors other than sugar-alcohol accumulation in nerve. We postulate that endoneurial hypoxia may produce many of the observed morphological and biochemical changes in experimental diabetic neuropathy.

INTRODUCTION

The cause of the distal symmetrical polyneuropathy which is the commonest peripheral nerve disorder in patients with diabetic mellitus is unknown. Studies on the nerves of diabetic animals have revealed both morphological and neurophysiological abnormalities confirming that such animals also develop a predominantly distal peripheral neuropathy (Eliasson, 1964; Sharma and Thomas, 1974; Jakobsen, 1976*a*, *b*, 1978; Chopra *et al.*, 1977; Brown *et al.*, 1980; Brismar and Sima, 1981).

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Biochemical abnormalities have been found in the nerves of animals with experimental diabetes which suggest a metabolic cause for diabetic peripheral neuropathy (Gabbay *et al.*, 1966; Stewart *et al.*, 1967; Greene *et al.*, 1975; Spritz *et al.*, 1975).

Most, if not all of the biochemical abnormalities in experimental diabetic neuropathy could arise if oxygen (O_2) supply to nerve was impaired since nerve *in vitro* is largely dependent upon oxidative metabolism for energy production (Greene *et al.*, 1979). Thus reduced nerve myoinositol concentration (Greene *et al.*, 1975; Greene and Winegrad, 1981), decreased rate of synthesis and transport of intra-axonal proteins (Schmidt *et al.*, 1975; Sidenius and Jakobsen, 1981, 1982), reduced incorporation of glycolipids and amino acids into myelin (Spritz *et al.*, 1975) and excessive intracellular accumulation of glycogen (Powell *et al.*, 1977; Bestetti *et al.*, 1981; Moore *et al.*, 1981; Sima *et al.*, 1982), all of which have been documented in experimental diabetic neuropathy, could be due to a reduction in oxidative metabolism.

The supply of O_2 to nerve will be reduced if blood flow is reduced and if diffusion of O_2 from blood to cells is impaired. In the peripheral nerves of patients and animals with diabetes there is thickening of capillary walls and reduplication of capillary basement membranes (Fagerberg, 1959; Bischoff, 1973; Vital *et al.*, 1973; Schlaepfer *et al.*, 1974; Powell *et al.*, 1977; Yagihashi and Matsunaga, 1979; Yagihashi *et al.*, 1979; Sima, 1980; Sima *et al.*, 1982) which could reduce both nerve blood flow (NBF) and the rate of diffusion of O_2 from blood to cells. Two additional factors which could also impair delivery of O_2 to nerve in diabetes are blood hyperviscosity (Barnes *et al.*, 1977; Lowe *et al.*, 1980) and endoneurial oedema (Jakobsen, 1978).

In order to investigate the possibility of endoneurial ischaemia and hypoxia in diabetic neuropathy we have measured NBF and endoneurial O_2 tension (P_nO_2) in the sciatic nerves of rats with streptozotocin-induced diabetes and in healthy controls. Nerve blood flow was measured with the hydrogen (H_2) clearance technique (Aukland *et al.*, 1964). Platinum (Pt) microelectrodes were employed to measure endoneurial H_2 and O_2 using the principle of polarography (Silver, 1967). Both NBF and P_nO_2 were significantly decreased after four months hyperglycaemia.

Since endoneurial oedema and elevated endoneurial fluid pressure (EFP), which may be due to the accumulation of the sugar alcohol sorbitol, could theoretically contribute to the reduced NBF in the sciatic nerves of diabetic animals, we also measured NBF in the sciatic nerves of rats which had been fed a galactose-rich diet for approximately four months. In experimental galactose neuropathy, electrophysiological abnormalities are present and endoneurial oedema, EFP increase and sugar-alcohol (galactitol) accumulation are much more marked than in experimental diabetic neuropathy (Stewart *et al.*, 1967; Sharma *et al.*, 1976; Low *et al.*, 1980, 1982; Powell *et al.*, 1981; Low and Schmelzer, 1983). We were able to demonstrate only a minor reduction in NBF in these animals and conclude that increased EFP is not the major cause of the reduced NBF in experimental diabetic neuropathy.

METHODS

Sciatic nerve blood flow was measured in 8 rats with streptozotocin-induced diabetes and in 8 paired controls, and in 8 galactose fed rats and 8 paired controls. Endoneurial oxygen tension was measured in the diabetic rats and in their controls.

Experiments with Diabetic Rats

Sixteen adult Sprague-Dawley rats were weighed and anaesthetized with an intraperitoneal injection of pentobarbitone (50 mg · kg^{-1}). Caudal nerve conduction velocity was obtained by stimulating the tail distally and recording the compound nerve action potential at the proximal end of the tail using stainless steel needle electrodes. Latency was measured from the onset of the stimulus artefact to the onset of the compound nerve action potential. Conduction velocity was calculated by dividing the distance between active recording electrode and the stimulating cathode (exactly 8 cm) by the latency. The temperature of the tail was maintained at 35° C with a thermistor probe and infrared lamp. Eight of the rats (diabetic group) received an intraperitoneal injection of a solution of streptozotocin in 0.05 M citrate buffer at pH 4.5 (50 mg · ml^{-1}; dose 1 ml · kg^{-1}). The remaining 8 animals (control group) received an intraperitoneal injection of citrate buffer (1 ml · kg^{-1}) without streptozotocin. The rats were housed in cages with plastic floors covered with sawdust and wood shavings and were fed Purina Rodent Laboratory Chow (No. 5001) with an unrestricted supply of water.

Four months after injection, the rats were fasted overnight, weighed, examined and anaesthetized with an intraperitoneal injection of atropine (20 μg · kg^{-1}) and thiobutobarbitone sodium (Inactin, Byk Gulden Konstantz, West Germany). The dose of Inactin for the controls was 100 mg · kg^{-1}, and for the diabetics, 50 mg · kg^{-1}. The dose was chosen, from preliminary studies, to produce a similar depth of anaesthesia and maintain similar arterial blood gases and mean arterial pressure (MAP). Body temperature was monitored with an intra-abdominal thermistor probe and maintained between 36 and 38° C with an infrared lamp. A tracheostomy tube was inserted and the animals were allowed to breathe spontaneously. A polyethylene cannula, which was flushed with a solution of 0.9 g · dl^{-1} sodium chloride (NaCl) and heparin (2 U · ml^{-1}), was inserted into the left carotid artery. Mean arterial pressure was recorded from the carotid cannula with a pressure transducer (Statham P23dB, Puerto Rico) at the level of the heart and recorded on a chart recorder (Serco, Deerfield, Ill., USA). Arterial pH, and oxygen and carbon dioxide tensions (P_aO_2, P_aCO_2) were measured with a blood gas analyser (Radiometer BMS MK2, Copenhagen, Denmark) on 200 μl samples of arterial blood, most of which was injected slowly into the animal *via* the arterial cannula. The concentration of O_2 in the inspired gas was adjusted to maintain P_aO_2 at approximately 95 mmHg.

Blood flow was measured in the right sciatic nerve using the H_2 clearance technique. The nerve was carefully exposed and a small opening made in the epineurium. The preparation was covered with mineral oil, the temperature of which was maintained at 33.5° C with a thermistor and temperature controller (Bailey Instruments, NJ, model TCAT). Nitrogen (N_2) was bubbled through the oil at 3 to 5 ml · min^{-1}. The reference electrode consisted of a polyethylene tube (3 mm outside diameter) filled with 2 M KCl and 3 per cent agar which was sutured into the subcutaneous tissue of the abdominal wall. The other end of the tube was inserted into a flask containing 2 M KCl into which was also placed a silver-silver chloride (Ag-AgCl) electrode connected to the reference terminal of a current sensitive amplifier (Transidyne General Corporation, Ann Arbor, MI).

Platinum microelectrodes were constructed by soldering a 3 cm length of 10 μm diameter Pt wire to a 10 cm length of 0.2 mm diameter copper (Cu) wire which was placed inside a glass capillary (1 mm outside diameter, 0.5 mm inside diameter). This was pulled to a fine point with a vertical pipette puller (David Kopf Instruments, Model 700C, Tujunga, CA) and the tip, which contained the Pt wire, was bevelled to an angle of 30° C. The diameter of the tip was approximately 3 to 5 μm. The Cu wire was fixed to the open end of the capillary with epoxy cement and was connected to the input terminal of the current sensitive amplifier, the output of which was recorded on the second channel of the chart recorder. In order to calibrate the system, the microelectrode was placed in a solution of 0.9 g · dl^{-1} NaCl maintained at 33.5° C and polarized to 0.25 V with respect to the reference electrode. Calibration was performed for 0, 5 and 10 per cent H_2 and electrodes were rejected unless the current flowing in the circuit was directly proportional to the H_2 concentration. An electrode was inserted through the epineurial opening into the endoneurium and the baseline current allowed to stabilize. Five to 7 per cent H_2 was added to the inspired gas mixture and the O_2 and N_2 concentration adjusted to maintain a P_aO_2 of about 95 mmHg. When the H_2 concentration in the nerve was stable (indicating equilibrium with arterial blood), the H_2 supply was shut off and the N_2 concentration increased appropriately in order not to alter the P_aO_2. The H_2 clearance curve was recorded until the current reached baseline. The natural logarithm of the current recorded during the first 10 min of each clearance curve was calculated for every 30 s interval from the onset of H_2 washout. Blood flow was calculated from the slope of the line fitted to these data by the method of least squares (Aukland *et al.*, 1964). If the clearance curve had an initial fast component, the slope of the slow component only was used as the measure of NBF (Low and Tuck, 1984). Vascular resistance in nerve was calculated from the ratio of MAP to NBF.

After recording the H_2 clearance curve, the perineurium was carefully removed along 5 mm of the exposed nerve. The diameter of the desheathed segment was measured at three positions with a fine needle and a calibrated micromanipulator from which an estimate of the radius ($\bar{R}$) was obtained. A Pt microelectrode, similar to that described above, was polarized to -0.65 V and placed in a solution of 0.9 g · dl^{-1} NaCl maintained at 33.5° C through which was bubbled N_2, 90 per cent N_2 and 10 per cent O_2, or room air. Electrodes which generated a current which was proportional to the O_2 concentration were used to measure P_nO_2. The electrode was inserted into the nerve fascicle perpendicular to the central axis until the tip was a distance equivalent to $\bar{R}$ deep to the surface. When the current was stable, it was withdrawn a distance of 0.1 $\bar{R}$ every 30 s so that 11 measurements of P_nO_2 were obtained at 10 equal intervals along the radius of the fascicle. The electrode was recalibrated with N_2 and air and the process repeated 3 to 5 times, thereby obtaining a 33 to 55 measurement of P_nO_2 per nerve. If the calibration between recordings differed by more than 10 per cent the results were discarded. Arterial blood gases were checked between each run and MAP was monitored throughout. In preliminary experiments, we satisfied ourselves that the electrode was sensitive to P_nO_2 by having the animal breath 100 per cent O_2 and 100 per cent N_2. With the former, P_nO_2 began to increase after about 10 s and reached a new level (usually 50 to 70 mmHg) after 2 min. With the latter, P_nO_2 began to fall rapidly towards zero within several seconds. By bubbling N_2 through the oil surrounding the nerve we hoped to ensure that little or no O_2 entered the nerve by diffusion. After recording NBF and P_nO_2, caudal nerve conduction velocity was recorded as described above. Blood was drawn from the arterial cannula for measurement of plasma glucose, glycosylated haemoglobin (HbA$_{1C}$), haemoglobin concentration (Hb), and haematocrit (Hct).

Experiments with Galactose-fed Rats

Sixteen male Sprague-Dawley rats weighing approximately 250 g each were divided into two groups and housed in identical cages to those described above. Eight were placed on a diet containing 40 per cent galactose for sixteen to twenty weeks with an unrestricted water supply and 8 were fed the same diet without galactose for the same duration after which they were weighed, examined and anaesthetized with intraperitoneal Inactin (110 mg · Kg^{-1}) and atropine (20 μg · kg^{-1}). The rats were mechanically ventilated through a tracheostomy tube with a rodent respirator (Harvard Apparatus, Millis, MA) after receiving 2 U of curare *via* a cannula in the left jugular vein and 4 U intraperitoneally. A cannula was also inserted into the left common carotid artery, and MAP, arterial blood gases and NBF measured as described above.

Statistical Analysis

All statistical calculations were carried out on a Hewlett-Packard HP 9845T computer with Data Manipulation and Basic Statistics and General Statistics programs. Null hypotheses were rejected when $P < 0.05$. Results are expressed as mean ± SE of mean. Data were tested for normal distribution using the χ^2 goodness-of-fit test. Normally distributed data were compared using the two-tailed Student's t-test for paired samples. If the variances were significantly different, t′ was calculated instead of t (Snedecor and Cochran, 1967). Means of data which were not normally distributed were compared using the Mann-Whitney test (two-tailed).

RESULTS

Experiments with Diabetic Rats (Tables 1 and 2)

At the beginning of these experiments, there was no significant difference between the mean weight of the animals which received streptozotocin and citrate buffer and those which received buffer only. After four months, the two groups weighed

TABLE 1. MEAN NERVE BLOOD FLOW, VASCULAR RESISTANCE, ARTERIAL PRESSURE, WEIGHT, CAUDAL NERVE CONDUCTION VELOCITY, HAEMATOLOGICAL, AND BIOCHEMICAL DATA OF 8 DIABETIC AND 8 CONTROL RATS

	Diabetics	*Controls*
Nerve blood flow $(\text{ml}\cdot\text{min}^{-1}\cdot 100\ \text{g}^{-1})$	8.7 ± 1.3*	13.0 ± 0.8 ($P < 0.01$)
Nerve vascular resistance $(\text{mmHg}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}\cdot 100\ \text{g}^{-1})$	15.0 ± 1.2*	8.8 ± 0.7 ($P < 0.01$)
Mean arterial pressure (mmHg)	123 ± 7	112 ± 5 (n.s.)
Weight (g)		
At beginning of experiments	267 ± 9	262 ± 9 (n.s.)
4 months after streptozotocin	301 ± 14	416 ± 7 ($P < 0.00001$)
Caudal nerve conduction velocity $(\text{m}\cdot\text{s}^{-1})$		
At beginning of experiments	43.4 ± 1.6	45.1 ± 0.8 (n.s.)
4 months after streptozotocin	51.5 ± 1.2	61.5 ± 2.3 ($P < 0.01$)
Plasma glucose $(\text{mmol}\cdot\text{l}^{-1})$	26.6 ± 2.4	5.8 ± 0.2 ($P < 0.00001$)
Glycosylated haemoglobin (%)	13.9 ± 1.3	4.2 ± 0.5 ($P < 0.00001$)
Haemoglobin $(\text{g}\cdot\text{dl}^{-1})$	18.1 ± 0.3	17.0 ± 0.3 ($P < 0.025$)
Haematocrit (%)	51.7 ± 1.2	47.4 ± 1.1 ($P < 0.025$)
pH	7.37 ± 0.03	7.35 ± 0.01 (n.s.)
P_aCO_2 (mmHg)	38 ± 5	36 ± 2 (n.s.)
P_aO_2 (mmHg)	94 ± 1	95 ± 2 (n.s.)

* n = 7 (*see text*).

301 ± 14 g and 416 ± 7 g, respectively ($P < 0.00001$). All the streptozotocin-injected animals developed dense bilateral cataracts, polyphagia, polydipsia and polyuria. Many had poorly formed loose stools at various times during the four month period after streptozotocin injection. All had signs of muscle wasting but none had weakness or gait disturbance. The mean plasma glucose in the streptozotocin injected group was 26.6 ± 2.4 $\text{mmol}\cdot \text{l}^{1}$ (range 20.3–41.7) and in the controls was 5.8 ± 0.2 $\text{mmol}\cdot \text{l}^{-1}$ (range 5.3–7} ($P < 0.00001$). Mean $\text{HbA}_{1\text{C}}$, Hb and Hct were also significantly increased in the diabetic animals compared with the controls (Table 1). Mean arterial pressure, pH, P_aCO_2 and P_aO_2 of the two groups were not significantly different. Caudal nerve conduction velocity (CV) at the beginning of the experiments was the same in the diabetic group as in the controls. At the time of measurement of NBF and P_nO_2, CV was 51.5 ± 1.2 $\text{m}\cdot\text{s}^{-1}$ in the diabetic group and 61.5 ± 2.3 in the controls ($P < 0.01$).

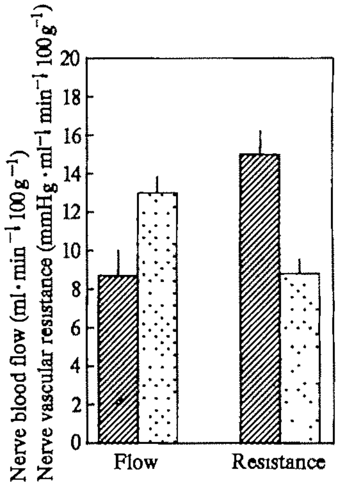

FIG. 1. Mean nerve blood flow and vascular resistance in 7 diabetic and 8 control rats (Bar = 1 SE of the mean). Hatched areas = diabetics. Dotted area = controls

Mean sciatic nerve blood flow in 7 of the diabetic animals was 8.7 ± 1.3 $\text{ml}\cdot\text{min}^{-1} . 100\ \text{g}^{-1}$ and in the 8 controls was 13.0 ± 0.8 $\text{ml}\cdot\text{min}^{-1}\cdot 100\ \text{g}^{-1}$ ($P < 0.01$) (fig. 1). In the remaining diabetic animal, the H_2 concentration in the nerve was insufficient after 1 h of breathing 10 per cent H_2 to record a satisfactory clearance curve. We interpret this as being indicative of very low blood flow. Increasing the inspired oxygen concentration of this animal to 100 per cent caused only a slight increase in P_nO_2 instead of the usual rapid rise to about 50 mmHg. This animal also had the highest plasma glucose (41.7 $\text{mmol}\cdot\text{l}^{-1}$). Nerve blood flow was within the normal range in only one animal. The mean sciatic nerve vascular resistance in the diabetics was 15.0 ± 1.2 $\text{mmHg}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}\cdot 100\ \text{g}^{-1}$ and 8.8 ± 0.7 in the controls ($P < 0.01$).

A total of 308 measurements of P_nO_2 was made in the sciatic nerves of the 8 diabetic rats and 286 in the controls. The mean P_nO_2 was 23 ± 2 mmHg in the former and 31 ± 2 in the latter ($P < 0.025$). The mean P_aO_2 during P_nO_2 recordings

TABLE 2. MEAN NERVE OXYGEN AND ARTERIAL TENSIONS, AND MEAN FASCICULAR RADIUS OF 8 DIABETIC AND 8 CONTROL RATS

	Diabetics	*Controls*
No. of P_nO_2 measurements	308	286
Endoneurial oxygen tension (mmHg)	23 ± 2	31 ± 2 ($P < 0.025$)
P_aO_2 (mmHg)	95 ± 1	95 ± 1 (n.s.)
Fascicular radius (μm)	450 ± 30	470 ± 35 (n.s.)

both in the diabetic rats and in the controls was 95 ± mmHg. The cumulative frequency of P_nO_2 measurements in intervals of 5 mmHg is shown in fig. 2. Sixty per cent of the P_nO_2 measurements were less than 25 mmHg in the diabetic group compared with 19 per cent in the controls. The mean P_nO_2 levels at the centre of the nerve fascicle and at 10 equal intervals between the centre and the surface are shown in fig. 3. There is very little difference in the P_nO_2 between one part of the nerve and another. In some nerves there was little variation in P_nO_2 between electrode position, while in others gradients of up to 15 mmHg were encountered. The mean fascicular radius for the diabetic group (450 ± 30 μm) and the controls (470 ± 35 μm) are not significantly different.

Experiments with Galactose-fed Rats (Table 3)

After sixteen to twenty weeks, the galactose-fed animals weighed 380 ± 6 g and the controls 433 ± 24 g. The difference is not significant. The galactose-fed animals developed dense cataracts and had diarrhoea but otherwise appeared to be healthy, without any sign of weakness or gait disturbance. They were clinically indistinguishable from our previous groups of galactose intoxicated rats (Low *et al.*, 1980,

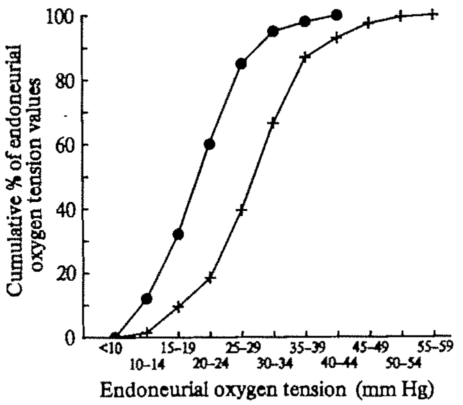

FIG. 2 Cumulative frequency of endoneurial oxygen tension measurements obtained from 8 diabetic (●) and 8 control (+) rats.

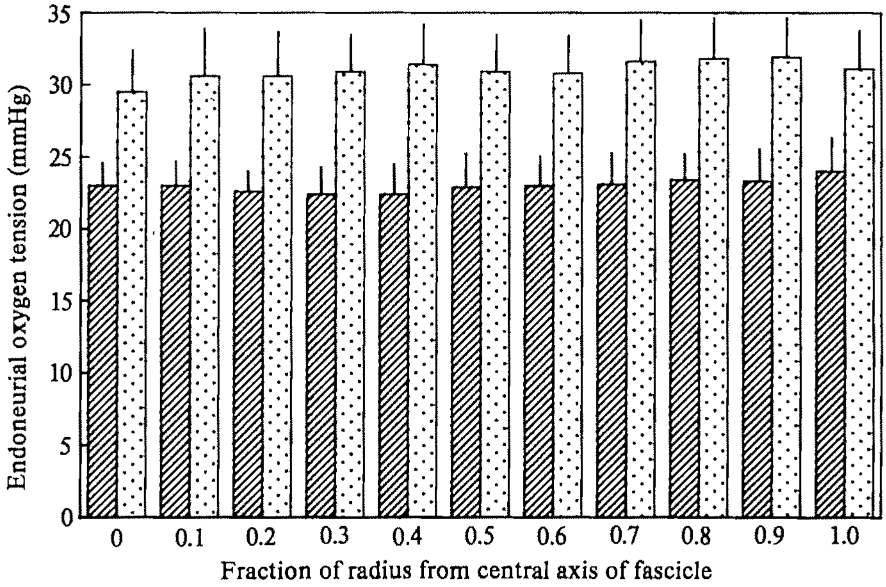

FIG. 3 Mean endoneurial oxygen tension in 8 diabetic and 8 control rats recorded at 11 equidistant points from the axis to the circumference of the nerve fascicle (Bar = 1 SE of the mean). Key as in fig. 1.

TABLE 3. MEAN NERVE BLOOD FLOW AND VASCULAR RESISTANCE, ARTERIAL PRESSURE, WEIGHT, AND BLOOD GASES IN 8 GALACTOSE-FED RATS AND 8 CONTROL RATS

	Galactose	*Controls*
Nerve blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	14.2 ± 2.5	17.0 ± 2.0 (n.s.)
Nerve vascular resistance ($mmHg \cdot ml^1\ min^{-1} \cdot 100\ g^{-1}$)	11.6 ± 1.6	8.4 ± 0.9 (n.s.)
Mean arterial pressure (mmHg)	140 ± 4	129 ± 3 ($P < 0.05$)
Weight (g)	380 ± 6	433 ± 24 (n.s.)
pH	7.37 ± 0.01	7.34 ± 0.01 (n.s.)
P_aCO_2 (mmHg)	38 ± 1	37 ± 1 (n.s.)
P_aO_2 (mmHg)	112 ± 4	114 ± 4 (n.s.)

1982; Low and Schmelzer, 1983). Mean arterial blood pressure in the galactose-fed animals was 140 ± 4 mmHg and in the controls was 129 ± 3 mmHg ($P < 0.05$). Arterial pH, P_aCO_2 and P_aO_2 did not differ significantly between the two groups. Mean NBF in the galactose-fed animals was 14.2 ± 2.5 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ and in the controls was 17.0 ± 2.0 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. The difference is not significant. Mean nerve vascular resistance in the galactose-fed animals was 11.6 ± 1.6 mmHg per $ml^1 \cdot min^{-1} \cdot 100^{-1}$ and in the controls was 8.4 ± 0.9 $mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100\ g^{-1}$ (fig. 4). The difference is not significant.

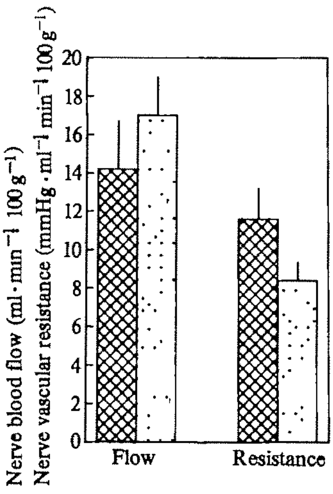

FIG. 4. Mean nerve blood flow and vascular resistance in 8 galactose-fed (cross hatching) and 8 control (dotted areas) rats (Bar = 1 SE of the mean).

DISCUSSION

Microelectrode and polarographic techniques were chosen for a number of reasons. The tip size of 3 to 5 μm minimized tissue damage. Hydrogen and oxygen polarography permitted multiple recordings *in vivo*. The choice of an appropriate polarization potential minimized interference by the opposite species (Aukland *et al.*, 1964). For instance Aukland *et al.* (1964) found that, employing the polarization potential that we used for hydrogen, an increase of pO_2 by 10 mmHg resulted in a reduction in hydrogen tension of only 0.15 to 0.40 per cent of saturation. Time required for equilibration was longer in diabetic rats. In one extreme case, both wash-in and wash-out were too slow to measure NBF accurately. In the other animals, the equilibrium value remained constant once it was attained and a monoexponential wash-out curve was obtained indicating that NBF was constant during the wash-out period. The NBF was calculated from the slow component of curves that were biexponential. Our reasons have been detailed (Low and Tuck, 1984). In brief, the reasons included (1) the mean flow in the nerves with monoexponential curves was similar to that of the slow component of those with biexponential curves; (2) the mean NBF computed from the slow component of 17 biexponential curves was 14.5 ± 0.7 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, very similar to values obtained in the sciatic nerve of the rat by other investigators using different techniques (Mandel *et al.*, 1963; Myers *et al.*, 1982; Sladky *et al.*, 1983); (3) the fast component is dependent on the closeness of the microelectrode tip to arterioles whereas the slow component is not (Hutten *et al.*, 1973); (4) in skeletal muscle, Aukland *et al.* (1964) found that the majority of H_2 clearance curves were biexponential, and that the slope of the slow component alone was a more accurate reflection of the blood flow measured directly from the venous outflow than was flow computed from both components; and (5) the flow calculated from the fast component of 118 ± 6 $\text{ml} \cdot \text{min}^{-1} \cdot 100\ \text{g}^{-1}$ appeared to be too rapid for any recognizable compartment of peripheral nerve. If we had derived our NBF values from both components, then NBF would be even more severely impaired in diabetic animals since they all had monoexponential curves (typical of NBF in hypoxia; Low and Tuck, 1984).

All 8 streptozotocin-injected rats developed diabetes which was confirmed by their weight loss, bilateral cataracts, and elevated plasma glucose and glycosylated haemoglobin concentrations. The 16 per cent reduction in mean caudal nerve conduction velocity in the diabetic animals is similar to the reduction in nerve conduction velocity in animals with diabetes reported by others (Eliasson, 1964; Miyoshi and Goto, 1973; Sharma and Thomas, 1974; Greene *et al.*, 1975; Jefferys *et al.*, 1978; Brown *et al.*, 1980; Sugimura *et al.*, 1980) and confirms the presence of a peripheral neuropathy in our animals.

We have shown for the first time that blood flow in the sciatic nerves of diabetic rats is at least 33 per cent less than that of healthy rats and that the endoneurial oxygen tension (P_nO_2) histogram in diabetic rats is shifted in the hypoxic direction. These findings are consistent with the hypothesis that diabetic peripheral neuropathy may be the result of endoneurial hypoxia. These findings have particular relevance since peripheral nerve, unlike most other tissues, does not autoregulate (Low and Tuck, 1984), so that it has very limited capability to compensate for reductions in blood pressure and oxygen delivery.

There exist several possible mechanisms for the observed reduction in NBF in experimental diabetes. A reduction in blood flow may be the result of a reduction in perfusion pressure or an increase in resistance to blood flow. In the diabetic animals, mean arterial pressure was slightly (but not significantly) higher than in the controls but nerve vascular resistance was almost double that of the controls. Such an increase in resistance could be due to a decrease in the number or calibre of patent endoneurial blood vessels or to an increase in blood viscosity.

It is likely that blood viscosity was increased in our diabetic animals. Two factors which could cause such an increase are the markedly elevated glucose concentration and the increased Hb and Hct. The last two may be due to dehydration but could also be a result of tissue hypoxia. Blood viscosity is increased in humans with diabetes with peripheral neuropathy but not in diabetics without complications (Barnes *et al.*, 1977). Hyperfibrinogenaemia also contributes to the increased viscosity of blood in diabetes (Barnes *et al.*, 1977; Lowe *et al.*, 1980). A reduction in erythrocyte deformability and an increase in erythrocyte adhesion to endothelial cells, which occur in patients with diabetes (Barnes *et al.*, 1977; McMillan *et al.*, 1978; Wautier *et al.*, 1981), could also increase resistance to NBF.

In both humans and animals with diabetes there is thickening of the walls and reduplication of the basement membranes of endoneurial blood vessels (Fagerberg, 1959; Bischoff, 1973; Vital *et al.*, 1973; Schlaepfer *et al.*, 1974; Powell *et al.*, 1977; Yagihashi and Matsunaga, 1979; Yagihashi *et al.*, 1979; Sima, 1980; Sima *et al.*, 1982). Such changes would be expected to result in increased resistance to blood flow and to impairment of diffusion of oxygen into the endoneurium.

It is possible that the accumulation of sorbitol in the nerves of diabetic animals (Gabbay *et al.*, 1966; Stewart *et al.*, 1967) might reduce NBF by increasing endoneurial pressure (EFP) as a result of an osmotic effect. Endoneurial oedema and increased EFP are found consistently in animals who have been fed galactose (Myers *et al.*, 1979; Low *et al.*, 1980) and are probably due to the accumulation of galactitol within the nerves by a process analagous to accumulation of sorbitol in the nerves of diabetic animals (Stewart *et al.*, 1967). Experimental galactose neuropathy (detected by slowing of nerve conduction velocity) begins within two to four weeks of galactose feeding (Gabbay and Snider, 1972; Sharma *et al.*, 1976) and persists throughout the period of galactose feeding (Sharma *et al.*, 1976; Low *et al.*, 1980). The present group of galactose rats most likely were neuropathic since they were studied at a similar time point and had similar clinical features to animals used in our previous studies (Low *et al.*, 1980, 1982; Low and Schmelzer, 1983) when abnormalities of nerve conduction and EFP were reported. As in these previous studies the sciatic nerve was swollen. The increase in nerve sugar-alcohol and water content and in EFP are much more marked in experimental galactose neuropathy than in diabetic neuropathy (Stewart *et al.*, 1967; Sharma *et al.*, 1976; Jakobsen, 1978; Powell *et al.*, 1981). Nerve blood flow in experimental galactose neuropathy was not statistically different from controls. MAP was slightly but significantly higher (by 8.5 per cent) in galactose rats, and since NBF autoregulates poorly (Low and Tuck, 1984), an argument can be made that galactitol accumulation is associated with a small reduction in NBF if MAP of galactose-fed animals is corrected to the control MAP value. This reduction is certainly not as great as in the diabetic rats and we conclude that accumulation of sugar alcohols, endoneurial oedema and increased EFP do not make a major contribution to the decrease in NBF which we observed in experimental diabetic neuropathy. However, the endoneurial oedema which occurs in experimental diabetic neuropathy (Jakobsen, 1978) could impair diffusion of O_2 from capillaries to Schwann cells and axons.

Endoneurial oxygen tension recorded *in vivo* has not been reported previously. In most nerves, P_nO_2 was fairly uniform at all electrode depths while in several nerves, gradients of up to 15 mmHg were observed between one electrode position and the next, presumably because of the proximity of capillaries to the electrode in certain positions. The distribution of P_nO_2 values is similar to that found in liver, brain, kidney and skeletal muscle (Schuchhardt, 1973). Mean P_nO_2 was significantly less in the diabetic animals than in the controls, and 60 per cent of the P_nO_2 measurements obtained from the diabetic animals were less than 25 mmHg, compared with only 19 per cent of those obtained from the controls. This finding suggests that the reduction in NBF in the diabetic animals is not simply an effect of reduced O_2 consumption of nerves of diabetic animals (Greene and Winegrad, 1981), since P_nO_2 would have been normal or increased if that were so (Bicher, 1974). It is more likely that NBF is reduced by one or more of the mechanisms outlined above and that the reduction in P_nO_2 is secondary to the reduction in NBF, and to a reduction in the rate of diffusion of oxygen through the thickened capillaries and increased volume of endoneurial fluid.

The P_nO_2 could be reduced if the oxygen-haemoglobin dissociation curve were shifted to the left. Although the concentration of HbA_{1C} and red-cell 2,3-diphosphoglycerate, both of which affect red cell oxygen affinity, are increased in diabetes, their net effect on the position of the oxygen-haemoglobin dissociation curve is too small to account for the low P_nO_2 in diabetic nerves (Ditzel *et al.*, 1973; Arturson *et al.*, 1974; Samaja *et al.*, 1982). Arterial pH, which also affects red cell O_2 affinity, was similar in the diabetic and control animals.

The relevance of nerve ischaemia and hypoxia to the pathogenesis of diabetic peripheral neuropathy remains to be determined. Frank infarction of nerve in animals with experimental diabetes has not been reported in peripheral nerve trunks but has been described in the ventral roots of the diabetic BB-Wistar rat (Sima and Thibert, 1982). Our observation that 60 per cent of P_nO_2 levels were lower than 25 mmHg in the nerves of diabetic animals may mean that a high proportion of axons and Schwann cells are chronically exposed to an environment in which oxygen tension is below the critical level (i.e. the pO_2 below which oxygen consumption falls below maximum). In such an environment, these cells would be unable to produce normal amounts of high energy compounds by oxidative metabolism and would presumably make relatively greater use of glycolysis for energy production as has been found in diabetic nerves *in vitro* (Greene and Winegrad, 1981). The accumulated intracellular glycogen in the nerves of diabetic animals (Bestetti *et al.*, 1981; Moore *et al.*, 1981; Sima *et al.*, 1982) may reflect decreased glucose utilization. An alternative role may be that of an energy store enabling nerve to adjust to anaerobic metabolism during ischaemic stress; this role may explain the resistance to ischaemic conduction block in diabetic neuropathy. The energy store concept has been proposed for the frog (Berthold, 1966) and aged rats (Grover-Johnson and Spencer, 1981).

The concentration of myoinositol is reduced in nerves of diabetic animals and correction of this by dietary supplements may restore nerve conduction velocity towards normal (Greene *et al.*, 1975), although this response has not been observed by some investigators (Jefferys *et al.*, 1978). The cellular uptake of myoinositol is partly energy dependent (Greene and Lattimer, 1982); hypoxia could account for this biochemical abnormality. Axonal transport is also energy-dependent and is impaired in nerves of diabetic animals in both anterograde and retrograde directions (Schmidt *et al.*, 1975; Sidenius and Jakobsen, 1981, 1982). This too might be due to the effect of hypoxia and might account for the axonal dwindling of nerves of diabetic animals (Jakobsen, 1976*a*; Sima *et al.*, 1982). The impairment of incorporation of lipids and amino acids into myelin in the nerves of diabetic animals (Spritz *et al.*, 1975) might also be due to endoneurial hypoxia and might contribute to some of the observed changes in myelin (Schlaepfer *et al.*, 1974; Jakobsen, 1976*a*; Powell *et al.*, 1977; Fukuma *et al.*, 1978; Sima *et al.*, 1982). Endoneurial hypoxia could explain the observed reduction in the activity of the sodium potassium pump in peripheral nerve in diabetes (Das *et al.*, 1976) which would account for the apparent increase in intra-axonal sodium (Brismar and Sima, 1981). Finally, similar voltage clamped single rat myelinated fibres studied under anoxic conditions (Brismar, 1981) reproduced the permeability changes and the shift to the inactivated state of the sodium channel previously reported for single nerve fibres from alloxan-induced diabetic rats (Brismar, 1979).

We conclude that the endoneurium of diabetic animals is relatively hypoxic as a result of reduced nerve blood flow and as a result of a decreased rate of diffusion of oxygen to tissue. Endoneurial hypoxia may account for some of the electrophysiological, biochemical and morphological abnormalities which have been observed in peripheral nerves of animals with experimental diabetes.

ACKNOWLEDGEMENTS

This work was supported in part by funds from NINCDS (NS 14304, RO1 NS1 7891) and Mayo Funds. R. R. Tuck was in receipt of a Thomas and Ethel Mary Ewing Scholarship in Medicine (University of Sydney, New South Wales, Australia) and a Fulbright Postgraduate Student Grant.

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(Received November 10, 1983. Revised January 12, 1984)

Brain (1984), **107**, 951-964

BILATERAL OPTIC NEURITIS

A LONG-TERM FOLLOW-UP

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SUMMARY

We have endeavoured to determine the fate of the adults and children presenting with bilateral optic neuritis who were reported by Hierons and Lyle (1959) and Meadows (1969). We have follow-up information from a variety of sources on 31 of the 34 adults for up to thirty-seven years, and on 17 of 19 children after up to thirty-two years. Three adult cases were excluded after review. The visual prognosis was variable in the adults but excellent in the children. None of the children has developed clinically definite multiple sclerosis. Two of the 11 adults with simultaneous bilateral optic neuritis developed multiple sclerosis, compared with 8 of 20 with sequential optic neuritis. We conclude that the risk of developing multiple sclerosis after simultaneous bilateral optic neurities in childhood is low; in adult life it is probably higher, but some patients even after more than two decades have no clinical evidence of the disseminated disease. Bilateral optic neuritis is aetiologically and prognostically diverse.

INTRODUCTION

The prognosis for vision and for the subsequent development of multiple sclerosis (MS) after unilateral optic neuritis has been the subject of numerous investigations. The prognosis for vision is generally good. The prognosis for the later development of MS is variable, the published incidence ranging from 13 to 85 per cent (McAlpine, 1964; Kurland *et al.*, 1966). In the United Kingdom the overall risk lies between 40 and 60 per cent, although there is evidence that the higher figures are more likely to reflect the true incidence (Lynn, 1959; McAlpine, 1964; Bradley and Whitty, 1968; Hutchinson, 1976; Compston *et al.*, 1978; Perkin and Rose, 1979; McDonald, 1983). Bilateral optic neuritis is less common and has received less attention. We have therefore reviewed patients reported in two previously published investigations from the National Hospital for Nervous Diseases, London (Hierons and Lyle, 1959; Meadows, 1969). Here we describe observations on patients reassessed up to thirty-seven years after the original illness.

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PATIENTS

Forty-seven patients were reported by Hierons and Lyle in 1959 and the first author (R.H.) has kept in touch with and reexamined many of them in the ensuing years. In 1980/81 we reviewed the original case records and examined the majority of those still living; we endeavoured to ascertain the cause of death in those who were not. Additional data were available for the great majority of those who were alive at the time of the original report.

Thirty-four patients were classified by Hierons and Lyle as having bilateral optic neuritis commencing in adult life. We have follow-up information on all but 3. Of the original 34 patients, 3 were excluded for the reasons given in the Tables. Additional data from a variety of sources was available on 30 of the remaining 31 patients after up to 37 years. We reexamined 14 after 24 to 37 (mean 28.3) years. R.H. had further information derived from his own examination or from that of other medical attendants in another 6, making 20 patients with a follow-up of 0.5 to 37 years (mean 17.9 years). In the remaining 10, additional information was available from nonmedical sources, mostly through correspondence with the patients themselves (*see* Tables).

Hierons and Lyle (1959) also reported on 13 children. We were able to reexamine 7 in 1980/81 after a mean of 26.9 years and R.H. had further data from examination by himself or by other doctors on another 5. S. P. Meadows also reported on bilateral optic neuritis in childhood in the Doyne Lecture of 1969. Some of the patients were included in both studies. By comparing the initials of the cases we ascertained that there were in all 27 different patients. Dr Meadows, who retired some years ago, made available to us such notes as he still had. Unfortunately it was only possible to obtain the names of 6 patients from his study who were not included in that of Hierons and Lyle. We were able to contact all of them and to reexamine 5, bringing the total number of identifiable childhood cases whom we reexamined in 1980/81 to 12/19 and on whom we have medical follow-up data from all sources to 17/19 after a mean of 18 years.

The visual fields were plotted on the Bjerrum screen but in some patients reassessment was carried out in the home and their visual acuities were recorded using the Snellen chart. Good vision was defined as an acuity of 6/12 or better in at least one eye. Colour vision was assessed using Ishihara plates. The pattern reversal visual evoked potential (VEP) was recorded in some patients (Dr Catherine Storey). Three patients had moved to other countries and in these, information was obtained from the patients themselves, their own medical practitioner or their optician or ophthalmologist. We have retained the original classification of Hierons and Lyle (1959). In considering the diagnosis of MS the criteria of McDonald and Halliday (1977) have been used. To conform with modern custom we have numbered the patients in the Tables. The order in Heirons and Lyle (1959) has been retained to facilitate comparison between the findings at presentation and at follow-up. In the present paper the numbers of the groups and Tables correspond, whereas in the earlier paper the Table number was higher than the group number (i.e. Group I was summarized in Table 2, etc.).

RESULTS

Group I. Simultaneous Acute Bilateral Optic Neuritis (Table 1)

The visual loss in the patients in this group began acutely and worsened rapidly in the course of a week. There were 6 patients in the original group. One was a native of Ceylon who returned home and two-and-a-half years after the visual impairment developed a paraplegia which progressed to quadriplegia. He had died before the 1959 publication and was considered then to have suffered from neuromyelitis optica. There was no post-mortem examination. We have further follow-up information on all the other patients in this group after seventeen to thirty years. Two were available for reexamination in 1980/81.

Visual prognosis. The prognosis for visual recovery was variable. The 2 patients reviewed recently are left with significant visual handicaps. One has no perception of light in one eye and perception of hand movements in the other. The second has visual acuities of 6/60 and 6/36 and has only a small rim of preserved temporal vision in one eye and a less severe nasal field defect extending into the temporal quadrant in the other. There was good visual recovery at the 1959 follow-up in 3 further patients. Thus, overall useful vision returned to one or both eyes in 4/6 patients.

Neurological prognosis. There have been no neurological developments in any of the patients in this group. Case 1 was seen ten years ago, after twenty years, when she had normal vision. She has recently reported by letter that she is now 80 years of age and in excellent health, thirty-one years after the original illness. Case 3 had 2 episodes of right-sided weakness within six months of the optic neuritis. She was perfectly well fourteen years later and although she referred in correspondence to slight weakness of one leg, she continued to work as a missionary in North Africa until the age of 63. She died aged 76 years from an illness which included an acute onset of dysphasia and right-sided weakness in a setting of mild hypertension. It seems probable that her death was due to cerebral vascular disease. Whether the episodes of weakness represented manifestations of multiple sclerosis is unknown, but we have classified her as early probable/latent MS. If that is correct, the illness was clearly of the benign type (McAlpine, 1964). We have seen Case 4 on a number of occasions during the past ten years on account of cerebrovascular episodes associated with diabetes and hypertension. He is still alive aged 75 without any recovery of vision. Case 5 has also not changed during the past twenty-two years,

TABLE 1 ACUTE SIMULTANEOUS BILATERAL OPTIC NEURITIS

Case	*Sex*	*Age of onset (yrs)*	*Length of follow-up (yrs)*	*Comment*
1	F	49	20(31)	Last examined aged 71: no change. Patient reported by letter to be well at 80.
2	F	35	17	Last examined aged 52: no neurological developments. Excluded because of prior neurological episode.
3	F	51	0.5(14)	Early probable/latent (EP/L) MS. Died aged 76 probably from cerebrovascular disease.
4	M	47	27*	Now has cerebrovascular disease associated with diabetes and hypertension.
5	M	34	26*	No neurological developments.
6	M	44	3	Died of 'neuromyelitis optica' by 1959.

Figures in brackets indicate length of follow-up when information was not from a doctor. * Patients personally reexamined in 1980/81.

namely twenty-six years after the episode of optic neuritis. In retrospect Case 2 should not have been included since there was a history of an episode of weakness in one arm eighteen years before the onset of visual symptoms.

Group II. Progressive Simultaneous Bilateral Visual Loss over a Period of up to Six Months (Table 2)

This group was made up of 7 patients in whom there was progressive deterioration of vision simultaneously in both eyes for up to six months. Six of the 7 were adults at presentation. Case 8 was aged 15½ years at onset: he has been retained in this group since the 19 childhood cases were less than 15 years old at presentation, and in addition the progressive nature of the visual loss distinguished him from the younger patients. All patients have been seen since the 1959 publication and the length of follow-up at the last examination is shown in Table 2. Four were available for review in 1981. When Case 10 was reviewed she said that so far as she could recollect, thirty years later, the visual deterioration had occurred over a rather shorter period than stated in the 1959 report. Reexamination of the original notes from King's College Hospital revealed that both eyes were affected within 3½ weeks and that the maximal visual deterioration was reached within four weeks on one side and one week on the other. She would thus have been more appropriately placed in Group III.

Visual prognosis. After nine to thirty years, only 2 of the 7 patients (or 1 out of 6, if Case 10 is excluded) recovered good vision. The others were left with acuities ranging from 6/18 to perception of light. In 3 of the 4 patients reviewed in 1980/81,

TABLE 2. PROGRESSIVE SIMULTANEOUS BILATERAL OPTIC NEURITIS

Case	*Sex*	*Age at onset (yrs)*	*Length of follow-up (yrs)*	*Comment*
7	F	43	25*	No neurological developments. Delayed VEP.
8	M	15.5	30*	No neurological developments. Delayed VEP.
9	F	25	26*	No neurological developments.
10	F	28	30*	MS.
11	M	64	9(13)	Died of a stroke aged 77. No other neurological developments. Last reviewed by R.H. in 1973.
12	M	32	30	Seen at the Middlesex Hospital, 1976–1978. No neurological developments. Died of a myocardial infarction.
13	M	20†	15(27)	No neurological developments 15 yrs later when reviewed by S. P. Meadows. Died from myocardial infarction 27 yrs after onset.

† Age given in 1959 was misprinted. * As for Table 1.

field defects were present as follows: arcuate scotoma, peripheral constriction and dense central scotomata. All 3 had optic atrophy and colour vision defects. The acuities of Case 10 at the present review were 6/6 bilaterally, and colour vision, fields and fundi were normal.

Neurological prognosis. As in Group I, the long-term prognosis was good. Three of the patients have died probably from vascular disease. Case 11 remained well for thirteen years after the onset and then at the age of 77 developed a sudden hemiplegia and died within two days. Case 12 died thirty years after the onset of visual symptoms, at the age of 62, probably from a myocardial infarction. During the last few years of his life he had developed hypertension and was seen at hospital, but there were no neurological developments during his lifetime. Case 13 died aged 58 from a myocardial infarction. The indications are that for twenty-seven years he had remained well apart from visual impairment and there were no neurological developments during these years.

Cases 7 to 9 when reexamined in 1980/81 had shown no clinical change since the 1959 report. Case 10 at the time of our earlier account had had a right extensor plantar response and this had earlier been bilateral. When seen recently she described an episode four years previously (when aged 54) in which the left leg became heavy and dragged over many months, but subsequently improved. On examination there are now bilateral extensor plantar responses and brisk tendon reflexes. She thus fulfils the criteria for clinically definite multiple sclerosis which is clearly of the benign type.

Group III. Bilateral Sequential Optic Neuritis with an Interval of 1 to 3 Months (Table 3)

This group was made up of 9 patients in whom the eyes were involved sequentially in one to three months. We have further information on all but 2 of the patients.

TABLE 3 SEQUENTIAL OPTIC NEURITIS WITHIN 1 TO 3 MONTHS

Case	*Sex*	*Age at onset (yrs)*	*Length of follow-up (yrs)*	*Comment*
14	M	24	8(17)	Said to be well 17 yrs later.
15	F	27	25*	No neurological developments.
16	F	19	29*	Excluded (choroidoretinitis).
17	F	20	15	MS—died.
18	M	48	6	Emigrated to Canada. Lost to follow-up.
19	F	28	27*	No neurological developments.
20	M	21	2	Lost to follow-up by 1959.
21	F	38	4(26)	Reported from Canada in 1980/81 that she was well. Ophthalmologist reported that the vision and fields were normal.
22	M	41	3.5	MS—died before 1959 report.

* As for Table 1.

Three were available for review in 1980/81. Case 16 has been excluded because at review she was found to have choroidoretinitis involving the macular areas.

Visual prognosis. The 3 patients examined in 1981 had all recovered to acuities of 6/12 or better. Visual field defects were present in 3 of 6 eyes and the abnormalities included a temporal field defect, a peripheral quadrantic defect and a temporal field defect extending to central vision. Only 1 patient did not have optic atrophy. Of the remaining 4 patients known to be alive in 1959, vision had returned to 6/9 or better in at least one eye at the latest follow-up. Case 22, who had died before 1959, had shown no visual recovery after 3.5 years.

Neurological prognosis. Two of the 8 patients remaining in this group have developed MS. Case 22 was known to have done so in 1959 and Case 17 was suspected as having MS then. She died at the age of 34 years. The visual loss occurred with an interval of five weeks between the involvement of each eye and later recovered to acuities of 6/6 and 2/60. She remained well for fifteen years and then developed weakness of both legs and died within a few weeks. Visual acuity in the final illness seems to have been similar to that in our 1959 account. Necropsy revealed extensive demyelination in both cerebral hemispheres and a large diffuse area of demyelination in the thoracic spinal cord extending over many segments. The optic nerves were not examined. The other patients in Group III were virtually unchanged from 1959 and were without neurological signs.

Group IV. Bilateral Sequential Optic Neuritis with an Interval of More than 3 Months (Table 4)

This group was made up of 11 patients in whom the eyes were involved with an interval of greater than three months. Additional information is available on all but one in whom the diagnosis of MS had been established in 1959. Five were available for reexamination in 1980/81 and we have spoken with a sixth on the telephone.

Visual prognosis. Case 25 when last seen six years after the onset of visual disturbance had VR 6/36 and VL 6/60. The vision recovered to 6/12 or better in at least one eye in 7 of the 11 patients. In the remainder, acuity varied from 6/12 to hand movements.

Neurological prognosis. Cases 25 and 27 had been diagnosed as suffering from MS in 1959. Case 30 died at the age of 63 and had difficulty in walking in the latter part of his life. We did not see him during this stage, and the cause of the gait disturbance is thus not known. We have classified him as having early probable/latent MS although there was evidence of hypertension and cardiac enlargement so that the diagnosis of cerebral vascular disease is possible. Case 28 committed suicide at the age of 63 and there is no evidence to suggest that he had developed multiple sclerosis. Case 33 was reviewed when he was 55, nineteen years after the first visual episode, and there had been no neurological developments. He died suddenly from a heart attack aged 66. A social worker reported that he was perfectly well apart from the visual disturbance until his death. Case 29 was diagnosed as suffering from

TABLE 4. SEQUENTIAL OPTIC NEURITIS, INTERVAL > 3 MONTHS

Case	*Sex*	*Age of onset (yrs)*	*Length of follow-up (yrs)*	*Comment*
23	M	52	31*	No neurological developments. Gross bilateral delay in VEP.
24	F	46	24*	No neurological developments.
25	F	41	6	MS in 1959. Lost to follow-up.
26	F	44	26*	No neurological developments.
27	M	42	5	MS. Died in 1959.
28	M	36	7(27)	Suicide aged 63. No neurological developments. (Information from relatives and coroner's inquest records.)
29	M	46	30*	EP/L MS.
30	M	36	7(27)	EP/L MS. Died aged 63, ?cerebrovascular disease.
31	M	49	2(30)	Excluded because of prior neurological episode.
32	M	29	37*	MS.
33	M	36	19(30)	No neurological developments. Died from 'heart attack'.

* As for Table 1.

'possible' MS in 1959 because of a transient episode of weakness and numbness in one arm a year after the visual symptoms. In 1981 he was 76 years of age and there were no abnormal neurological findings, thirty years after the optic neuritis. In order to avoid underestimating the risk of MS we have classified him as early probable/latent MS. We have not seen Case 31, but he reports on the telephone that he is now 79 and living an independent life without significant handicap apart from the impaired vision now present for thirty years. Multiple sclerosis had already been diagnosed in 1959; it is clearly of the benign type. Review of the original notes disclosed that two years before the optic neuritis he had had an episode of numbness of the right upper lip and Lhermitte's symptom lasting a few weeks. He has therefore been excluded. Case 32 was also regarded in 1959 as possibly suffering from MS. Seventeen years later he developed fairly acute vertigo. He was admitted to hospital in Cardiff; the case notes recorded dysarthria, nystagmus on right lateral gaze, impaired coordination in right arm and both legs, with normal tendon reflexes and flexor plantar responses. At the present review he had mild weakness of left hip flexion, with increased tendon reflexes and an extensor plantar response in that limb. We have accordingly classified him as clinically definite MS, again of the benign type. The other patients in Group IV have not changed and there have been no neurological developments.

TABLE 5 BILATERAL OPTIC NEURITIS NUMEROUS ATTACKS

Case	*Sex*	*Age of onset (yrs)*	*Length of follow-up (yrs)*	*Comment*
34	M	23	32*	No neurological developments. Delayed VEPs.

* As for Table 1.

Group V. Bilateral Optic Neuritis, Numerous Attacks (Table 5)

There was one patient in this group. At the age of 23 years he developed the first of many attacks of optic neuritis affecting either eye. He recovered incompletely from the first episode. Subsequent attacks occurred every three to four months for the next seven years but tended to recover to the original deficit. The last attack was simultaneously bilateral. In 1980/81, twenty-five years after the last attack, visual acuity was VR 6/12 and VL 6/24. Bilateral centrocaecal scotomata extending into the temporal fields and bilateral optic atrophy were present. There have been no other neurological developments.

TABLE 6. CHILDHOOD CASES (HIERONS AND LYLE, 1959)

Case	*Sex*	*Age at onset (yrs)*	*Length of follow-up (yrs)*	*Comment*
35	M	7	(2)	Lost to follow-up. Father reported that he was normal 2 yrs later.
36	F	12	2(13)	Lost to follow-up. Friends reported 13 yrs after that she was well.
37	F	9	0.5(28)	Contact by letter: well. Optician: normal acuity, pale discs.
38	M	8	9(20)	Priest reported after 20 yrs that he was normal.
39	F	8	32*	Acute disseminated encephalomyelitis. No neurological developments.
40	M	8	5(28)	Mother states that he is perfectly well and at present working on an oil rig.
41	F	6	21*	No neurological developments.
42	F	8	3(10)	Well—no neurological developments.
43	F	5.5	23*	Well—no neurological developments.
44	F	7	25*	Well—no neurological developments.
45	F	6	30*	Well—no neurological developments.
46	F	8	31*	Well—no neurological developments.
47	F	7	26*	Well—but poor L. vision. EP/L MS.

* As for Table 1.

Group VI. Childhood Cases (Tables 6 and 7)

There were 19 identifiable patients in the reports of Hierons and Lyle (1959) and Meadows (1969). All were under 15 years of age at presentation.

Visual prognosis. The visual prognosis was excellent. No patient was visually disabled after up to twenty-five years in the Meadows' series. Eleven of the 12 patients who were reexamined had been seen originally at the height of the visual symptoms. With the exception of a single eye, disc swelling had been present in all. Peripapillary nerve fibre layer haemorrhages were present in 4 patients. The majority had severely impaired vision at the onset and 10 were virtually blind. One eye did not recover beyond 6/60 but in all others the acuity was 6/9 or better. The visual fields were normal in 10 patients. An extensive central scotoma was found in one eye but the remainder of the field defects were mild and included a temporal paracentral scotoma (1 eye) and concentric peripheral field defect (2 eyes). Colour vision was assessed in 10 patients and was abnormal in 4 (7 eyes). Optic atrophy was present in all patients but one.

The VEP was recorded in 8 patients, and was normal in 5. One further patient has an equivocal delay in one eye following half-field stimulation but the VEP was otherwise normal. In the other 2 patients the VEP was delayed and of abnormal waveform in both eyes.

Neurological prognosis. The neurological prognosis was excellent. Only Case 47 has had a further neurological episode—tingling affecting all 4 limbs while taking antidepressants eight years ago. Examination in 1982 revealed no abnormal neurological signs apart from optic atrophy. The significance of that episode is uncertain but as the criteria for early probable/latent MS are fulfilled she has been classified accordingly. In Meadows' series there had been no new neurological developments after 'less than three ' to eighteen years in 1969. There have still been no neurological developments in any of the 5 cases reexamined in 1981.

Case 39 from Hierons and Lyle's series requires further comment. She had evidence of more diffuse neurological involvement at the onset. She was classified in 1959 as 'probable' MS but on review she seems more likely to have been an example

TABLE 7 CHILDHOOD CASES (MEADOWS, 1969).
CASES IDENTIFIED WHO WERE NOT INCLUDED BY HIERONS AND LYLE

Case	*Sex*	*Age at onset (yrs)*	*Length of follow-up (yrs)*	*Comment*
48	M	7	14*	Well—no neurological developments.
49	M	11	25*	Well—no neurological developments.
50	F	9	19*	Well—no neurological developments.
51	F	11	16*	Well—no neurological developments.
52	M	7	25*	Well—no neurological developments.
53	F	8	(20)	Reported to be normal by her father.

* As for Table 1.

of acute disseminated encephalomyelitis. When aged 14 years she developed headache, vomiting and generalized convulsions. Two weeks later she complained of diplopia and developed acute bilateral visual failure. The visual acuities were 3/60 and 6/18 and mild bilateral swelling of the optic discs was present. A diffuse nonspecific slow wave abnormality was present in the EEG. Vision improved over the next two to three months but intellectual impairment was now present and epilepsy persisted. Reassessment twenty-five years later shows moderately severe intellectual impairment and epilepsy, requiring long-term institutional care. The visual acuity is 6/9 in each eye and the visual fields and optic fundi are normal.

DISCUSSION

The prognosis both for vision and for the subsequent development of multiple sclerosis is clearly different in adults and children and it is convenient to consider them separately.

In children, the visual prognosis was excellent, only 1 eye having a poor residual acuity, although the optic discs were pale in all but one patient. The risk of developing multiple sclerosis was also low. There was only a single rather doubtful case amongst the 17 of the total of 19 patients on whom there was follow-up data after a mean of eighteen years. It is of course possible that some of those with a short length of follow-up may have developed multiple sclerosis since, and that others may yet do so. But there is clearly a difference, at least in the risk of development of multiple sclerosis, between these children and adults who have had a unilateral attack of optic neuritis (McDonald, 1983). Further support for this view comes from the description by Meadows (1969) of 11 adults seen in the course of routine neurological practice in whom it was possible to make a retrospective diagnosis of 'abrupt' bilateral optic neuritis in childhood. Eight had made a reasonably good visual recovery and none had developed MS after a follow-up period of three to fifty-eight years. Although a contrary view was expressed by Kennedy and Carter (1961) the differences in their study may be more apparent than real. They found 8 cases of MS amongst 30 patients with optic neuritis presenting in childhood (*see* Kennedy and Carroll, 1960). If their unilateral cases are excluded, 18 bilateral cases remain. Three of them were later diagnosed as MS, but 2 of these patients had had neurological episodes preceding the presentation with bilateral optic neuritis. Thus only one of the remaining 16 cases developed MS.

We conclude that MS is uncommon after bilateral optic neuritis in childhood. Kennedy and Carter's evidence suggests that it may be more common after unilateral optic neuritis and Meadows (1969) noted that in 5 cases of multiple sclerosis first seen in adult life, there was a history of unilateral optic neuritis between the ages of 12 and 16 years.

What is the cause of bilateral optic neuritis in childhood if it is not multiple sclerosis? There is little doubt that one of our patients had acute disseminated encephalomyelitis, and the possibility arises that in some others optic neuritis may have been the predominant symptomatic manifestation of the same process. Such an interpretation is in keeping with the observation by Meadows (1969) that 'extensor plantar responses, usually bilateral were present in 9 out of 24, or slightly over one-third of the cases seen during the acute episode, and in 2 of these there was slight weakness of the lower limbs'.

It is of interest that the VEP was normal from two-thirds of the eyes recorded. A similar observation has been made in a new series of patients with bilateral optic neuritis seen originally at the Hospital for Sick Children, Great Ormond Street (J. Keast-Butler, C. Storey, D. Taylor, W. I. McDonald, unpublished observations). The VEPs were recorded at review nine months to fifteen years later. In all, 10 of the 18 patients had normal VEPs at follow-up. This contrasts with observations on adult unilateral optic neuritis in which 75 to 90 per cent of patients have delays (Halliday and McDonald, 1981). The reasons for the difference are uncertain. It is not simply attributable to a long follow-up, since two of the children in the Great Ormond Street series had normal VEPs after nine months and two years, respectively. It is possible that there is a greater potential for remyelination in childhood, and it is conceivable that the primary pathological process in some of the children is different from that in adults.

In adults the prognosis for vision was more variable. A poor visual outcome was the rule in the patients with simultaneous progressive visual loss. The patients with acute visual loss fared rather better, in keeping with the good prognosis generally observed in acute optic neuritis (Earl and Martin, 1967; Bradley and Whitty, 1967; Nikoskelainen, 1975; Gould *et al.*, 1977).

In considering the risk of developing multiple sclerosis in the adult patients it is appropriate to consider all the cases with a simultaneous onset (Groups I and II) together and to compare them with the pooled sequential cases (Groups III to V), because of the small numbers in each group. There were 20 patients (including Case 10 from Group II) with sequential optic neuritis, the incidence of clinically definite and early probable/latent MS in whom was 7/20 or 8/20 (if Case 30 in included) which is similar to the overall incidence of 40 per cent reported from London by Compston *et al.* (1978). Somewhat higher figures were reported for the same general geographical region by Bradley and Whitty (1968) (51 per cent) and Perkin and Rose (1979) (58 per cent). Hutchinson (1976) reported on overall incidence of 51 per cent in his series from Northern Ireland. In order to compare the incidence of MS in the present series with that of others from the UK, we have taken an overall figure of 50 per cent as being representative. Comparison of either the lower rate (7/20) or the higher (8/20) by the binomial test reveals no significant difference ($P_{(7/20)} = 0.132$; $P_{(8/20)} = 0.252$).

The incidence of multiple sclerosis after simultaneous bilateral optic neuritis in our study was appreciably lower. After the exclusions already discussed there was a total of 11 cases. Only 1 patient might be regarded as having developed clinically definite MS and one other as having early probable/latent MS. When these figures are compared with the previously published studies using the binomial test and the same assumption of 50 per cent incidence of multiple sclerosis after unilateral optic neuritis, the incidence in the bilateral cases is significantly less whether the higher rate (2/11) or the lower rate (1/11) is considered ($P_{(1/11)} = 0.006$; $P_{(1/11)} = 0.033$).

Our observations contrast with those of Hutchinson (1976) who found a higher incidence of MS in bilateral than in unilateral cases, and of Bradley and Whitty (1968) who found no difference between the two groups although they had only 5 simultaneous cases. The apparent discrepancy between our figures and those of Hutchinson (1976) are not attributable to differences in length of follow up (present series mean 17.9 to 28.3 years; Hutchinson mean 6.4 years). They probably arise in part from differences in the patient populations. The source of cases was different: the Northern Ireland patients came from a large general hospital whereas those in the present series came principally from a neurological hospital (National Hospital for Nervous Diseases) with strong referral links with a specialist ophthalmological hospital (Moorfields Eye Hospital). The age structure at onset was also different (present series mean 36.5 years; Hutchinson mean 26 years) and the sex ratio was different (present series F : M = 0.6 : 1, Hutchinson 4.4 : 1). Finally, Hutchinson's series contained an element of selection in that it was based not only on the follow-up of patients presenting with bilateral optic neuritis but on patients who already had MS in whom it was determined retrospectively that they had presented with optic neuritis.

Alternative diagnoses should be considered in Groups I and II. Some of the patients may have had Leber's optic atrophy although patients with a family history were excluded in the original study and at the recent review no further family members had been affected. The possibility of 'sporadic' Leber's disease nevertheless remains in a few patients, particularly the male Cases 4 and 5 in Group I who had acute and lasting bilateral visual loss.

The clinical course of the patients in Group I bears some resemblance to that of the children—the visual loss was simultaneous and reached its maximum in under a fortnight. Two patients (Cases 1 and 3) had immediately preceding fevers and like the children made a good visual recovery. As in the case of the children, the possibility arises that some of the patients in Group I may have had a restricted form of acute disseminated encephalomyelitis.

A striking feature of this investigation is the small proportion of patients with simultaneously bilateral optic neuritis who subsequently developed clinically definite MS. It is well known that lesions characteristic of MS can be found postmortem in patients without a history of neurological symptoms (Phadke and Best, 1983) and it is therefore possible that the true incidence of MS is higher than it seems. It is worth noting, however, that in all the adults who have not developed clinically definite MS the latest information concerns their status over the age of 60, apart from one patient who is in the sixth decade. It is clear that if some of these patients have MS, the illness is running a benign course. The factors which influence the course of MS and those which determine whether patients with optic neuritis will later develop the disease are not fully understood. In the United Kingdom the risk of developing MS after optic neuritis is higher in patients who are HLA-DR2 positive (Compston *et al.*, 1978; McDonald, 1983). There is also evidence that the presence of the allele BfS increases the risk of developing multiple sclerosis (Fielder *et al.*, 1981). This has led to the suggestion that while HLA-DR2 (or something in linkage disequilibrium with it) may confer susceptibility to neurological damage, the alleles of the Bf locus may influence the dissemination or rate of accumulation of further lesions. This hypothesis is being tested, but at present it is not possible to give an accurate prognosis in the individual case.

ACKNOWLEDGEMENTS

We are grateful to Dr S. P. Meadows for making available to us information about the patients he reported in his Doyne Lecture of 1969, and to Dr G. Barrett for statistical advice.

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(*Received April 19, 1983. Revised February 23, 1984*)

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INTERLIMB COORDINATION OF POSTURE IN PATIENTS WITH SPASTIC PARESIS

IMPAIRED FUNCTION OF SPINAL REFLEXES

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SUMMARY

Activation of leg musculature on both sides following a unilateral displacement was studied during stance on separate see-saws, or on stable force-measuring platforms, in patients with spastic hemiparesis and paraparesis. During balancing the movements on the spastic side were damped and the degree of muscle activation reduced. Whereas in healthy subjects the tibialis anterior muscles of both sides were activated, following a unilateral displacement, with the same strength and latency (see-saws 55 ms, platforms 85 ms), in hemispastic patients the EMG responses were delayed (by about 20 to 30 ms) and of reduced strength on the spastic leg, irrespective of whether the unaffected or the spastic side was displaced. In addition, the compensatory movements on the spastic side were damped in both conditions, although the amplitude of displacement was the same bilaterally. Although there was no correlation between the delay and the reduction in EMG response, the latter was correlated with the severity of paresis. In patients with spastic paraparesis quite similar results were obtained with delayed and reduced EMG responses on both sides. It is concluded that in spasticity the impaired regulation of quick compensatory movements is due to a dysfunction of a spinal interneuronal system by which the early EMG responses are mediated. This could be explained by loss of supraspinal control. In addition to the impaired neural activation of leg muscles, changes in the mechanical properties of muscle can be assumed to contribute to the damped movements on the spastic side.

INTRODUCTION

Neuronal regulation of upright stance is based on afferent signals from several sources (i.e. muscle proprioceptive, vestibular and visual systems). It is therefore not surprising that the clinical application of the Romberg test (1851) only rarely shows specific alterations in patients with lesions of the central or peripheral motor systems. However, when a displacement is induced during stance (Nashner *et al.*, 1979; Diener *et al.*, 1982) or gait (Nashner, 1980), functionally useful motor adjustments are elicited by proprioceptive signals to compensate body imbalance. Large body oscillations are therefore induced by such a displacement when postural

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reflexes mediating these adjustments are impaired, for example, in patients with cerebellar lesions (Mauritz *et al.*, 1979). Furthermore, in a condition in which subjects are displaced standing on an unstable platform (see-saw), more rapid regulation of leg muscle activation is required. This is provided by fast conducting spinal reflex pathways for posture stabilization (Dietz *et al.*, 1980). This mechanism is altered in patients with peripheral motor lesions, with consequent specific balancing abnormalities (Mauritz *et al.*, 1980).

The studies just cited were focused on the fast compensatory movements of a single limb. However, when body equilibrium is disturbed by a strong displacement of one leg, a fast bilateral regulation of leg muscle activation for load compensation is required. Recent studies in this field have provided evidence for a regulation of bilateral leg muscle activation at a spinal level (Dietz and Berger, 1982).

The aim of this investigation was to analyse the impairment of interlimb coordination in patients with a supraspinal lesion of the motor system to obtain information as to the influence of higher motor centres on the spinal coordinating mechanisms. In particular, an attempt was made to evaluate the way in which the contribution of spinal reflexes to the regulation of posture is altered in patients with spastic paresis.

METHODS

Patients and General Procedures

Fifteen normal individuals, 12 patients with spastic hemiparesis and 12 patients with spastic paraparesis were studied either while balancing on two separate see-saws or standing on force-measuring platforms. Most of the hemiparetic patients (7) had sustained a unilateral ischaemic infarction, while in the remainder there were various underlying causes (e.g. tumour, encephalitis). In patients with spastic paraparesis the lesion was most frequently due to cervical spondylotic myelopathy (6); in the remainder it was related either to myelitis (3) or was of unknown origin. The age of the patients ranged from 30 to 65 years (mean 46 years). The paresis had been present from between a few weeks to several years and in most of the patients spasticity was predominant, the paresis being only of minor significance. The patients were able to stand and walk unaided or with a little support.

Initially the subjects balanced, with their eyes open, for 90 s. Single supramaximal electrical stimuli (2 ms duration) were then randomly applied to the tibial nerve of either the spastic or the healthy leg. In further trials undertaken in 5 patients, one of the see-saws was suddenly tilted in an anterior direction, thereby mimicking mechanically the effect of the see-saw displacement that occurred following an electrical stimulation of the tibial nerve. The two see-saws were placed parallel and closely spaced on the two force-measuring platforms. The surface EMGs of tibialis anterior (TA) and gastrocnemius (GS) muscles of both legs were recorded by a telemetric device and the changes of angle in the ankle joints registered by a goniometer. The force changes in the anteroposterior direction exerted by the see-saws on the platforms were measured by 8 piezo-transducers fixed at the corners of each platform and transferred to a tape recorder (*see* fig. 1). During the balancing test it was continuously ascertained by a potentiometer that body weight was equally distributed between the two legs (i.e. between the two force-measuring platforms).

To compare the twitch contraction curves of triceps surae between the spastic and unaffected sides, the tibial nerve of each leg of patients with spastic hemiparesis was stimulated supramaximally. For this purpose the leg was immobilized between knee and ankle (knee angle 110 deg, ankle angle 90 deg), and the isometric force exerted by the triceps surae muscles recorded by a force transducer attached to the ball of the foot.

Data Processing

The EMG signals were filtered (time constant 3 ms) and transferred to tape for further off-line analysis (and for artefact control to an ink recorder). Following body displacements induced by electrical stimulation of one tibial nerve or by mechanically released see-saw excursions, the EMG responses were rectified and averaged by methods previously described (Dietz and Berger, 1982). The electrical stimuli or the platform force signals were used as a trigger, as appropriate, 10 trials being averaged in each case. For the analysis of the balancing movements on each side the spontaneous anteroposterior force fluctuations were separately recorded from each platform and further processed by a Fourier (FFT) analysis, using a balancing segment of 90 s duration (*see* Dietz *et al.*, 1980).

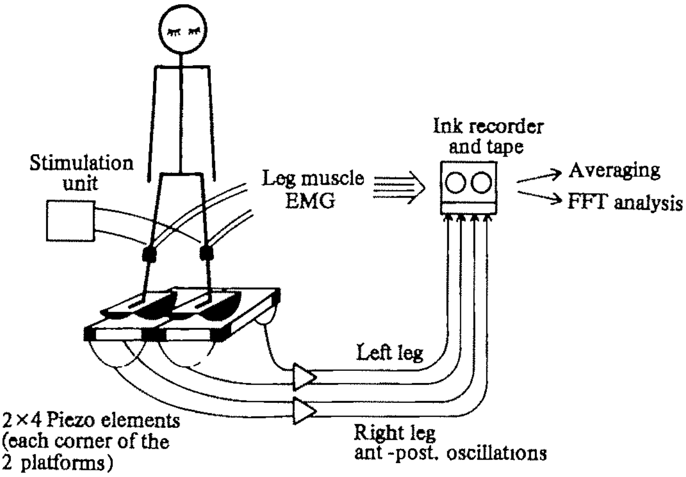
Stimulation unit
Leg muscle EMG
Ink recorder and tape
Averaging
FFT analysis
Left leg
Right leg ant-post. oscillations
2×4 Piezo elements (each corner of the 2 platforms)

FIG 1 Experimental conditions, showing the parameters recorded and analysed during balancing on two separate see-saws.

RESULTS

Spontaneous Balancing Movements

During balancing on two separate see-saws, anteroposterior balancing movements and the activation of homologous leg muscles in healthy subjects occurred quite synchronously on both sides with regard to timing and strength. Patients with spastic hemiparesis, tested under the same conditions, showed quite specific changes in their activity pattern and balancing movements on the spastic side, the latter being readily apparent from visual inspection. Fig. 2A shows an example of a patient with left spastic hemiparesis balancing on the two separate see-saws. This pattern was typical for the differences in muscle activation and balancing movements between the two sides, and occurred despite an equal distribution of body weight between the two see-saws. On the unaffected side, as expected, 4 to 5 Hz balancing oscillations were prominent, accompanied by corresponding short bursts of EMG activity. On the spastic side the anteroposterior balancing movements were damped and lower frequency balancing oscillations (below 1 Hz) were relatively prominent. Corresponding to this, the EMG amplitude was reduced, and the muscles showed mostly tonic activity, with an absence of short phasic EMG bursts. A synchronous activation of the homologous leg muscles occurred to the extent that periods of stronger activation on one side were connected with an increase of activity on the other.

The differences in the balancing movements between the healthy and the spastic sides were further studied by Fourier analysis. Fig. 2B shows that the overall shape of the power spectrum was similar on both sides, with no specific frequency range showing a marked increase or decrease on the spastic as compared with the

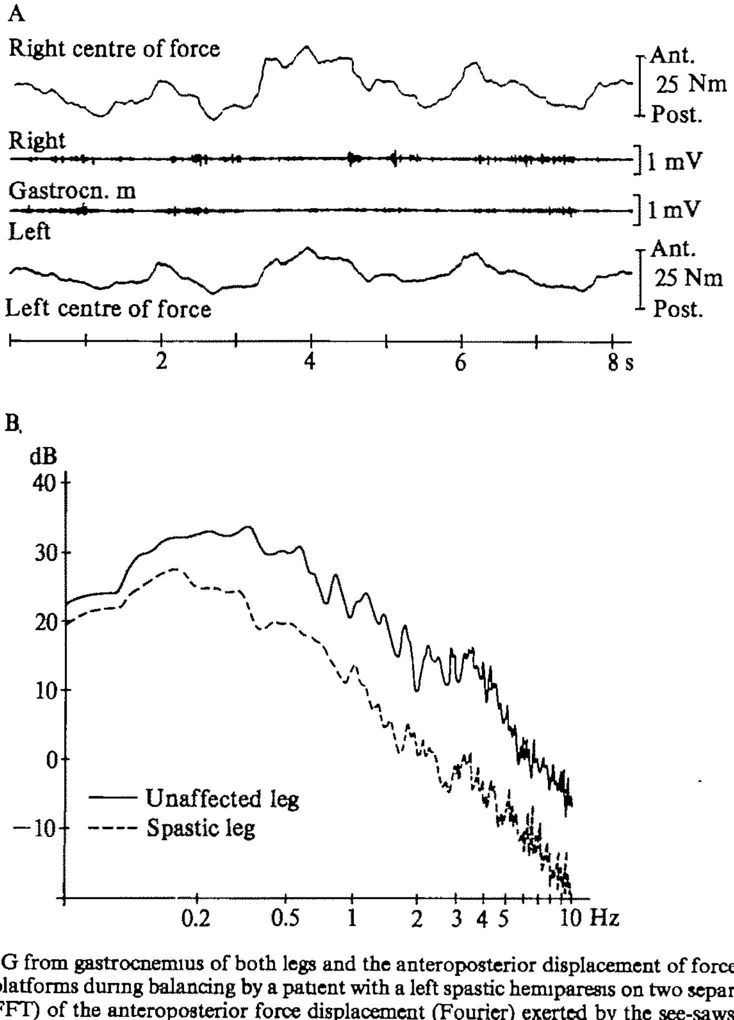

FIG 2. A, EMG from gastrocnemius of both legs and the anteroposterior displacement of force exerted by the see-saws on the platforms during balancing by a patient with a left spastic hemiparesis on two separate see-saws. B, power spectra (FFT) of the anteroposterior force displacement (Fourier) exerted by the see-saws on both sides. —— = unaffected leg. ---- = spastic leg.

unaffected side. On the spastic side, however, the oscillations at higher frequencies were relatively more reduced than those at lower frequencies. This corresponds to the visual observation of damped balancing oscillations.

Unilateral Displacement During Balancing

Spastic hemiparesis. The following experiments describe the postural EMG reactions following a unilateral displacement induced by electrical stimulation of one tibial nerve. The responses obtained in the hemiparetic patients were compared with the results gathered from 15 healthy subjects. The latter showed a bilateral EMG response in TA which appeared with the same latency (mean 55 ± 12 ms, *see* fig. 5) and amplitude on both sides following a unilateral displacement, whether this was induced by tibial nerve stimulation or by tilting one see-saw in an anterior direction. When the tibial nerve was stimulated submaximally so that no visible displacement was induced, no EMG responses followed the stimulus.

Because these bilateral EMG responses were obtained whether one or both legs were displaced by tibial nerve stimulation, the patients with spastic hemiparesis were displaced unilaterally, on the spastic side as well as on the unaffected leg. The mechanical and EMG responses of the two sides following unilateral foot displacement of a patient with left spastic hemiparesis are shown in fig. 3 in the form of averaged recordings.

Stimulation of the tibial nerve on the healthy right side produced a rapid anterior tilt of the right see-saw which was followed by activation of the ipsilateral TA about 50 ms later with a short phasic EMG burst (of about 200 ms duration), followed by prolonged tonic activity. As seen in the force trace, the foot was quickly dorsiflexed by the first burst of activity (fig. 3, upper traces). On the nondisplaced spastic side, the EMG activity in TA appeared later (about 20 ms) and with a reduced amplitude.

When the spastic side was displaced unilaterally by tibial nerve stimulation, an earlier activation of TA again occurred on the nondisplaced unaffected side. The difference in onset latency of the TA responses between the two sides was about the same as that seen when the unaffected leg was displaced by tibial nerve stimulation. In comparison with stimulation of the unaffected side, the amplitudes of the TA responses on the affected and the unaffected sides were reduced, the latter usually to about one-third of normal strength (fig. 3, lower traces). Similar EMG responses were obtained when one see-saw was tilted in an anterior direction.

The latency of the H reflex, measured over the GS muscle, and peroneal nerve conduction velocity were the same on both sides so that this difference in the latency of EMG responses cannot be explained by slower nerve conduction velocities on the spastic side. When the TA and GS muscles of relaxed limbs were stretched passively, biphasic potentials appeared with a latency of about 40 ms. This was also true for a further 4 patients tested.

Extreme differences in the amplitude of EMG responses after a unilateral displacement were observed in the few patients with predominant paresis (most of them were studied only a few weeks after the occurrence of the cerebral lesion). In

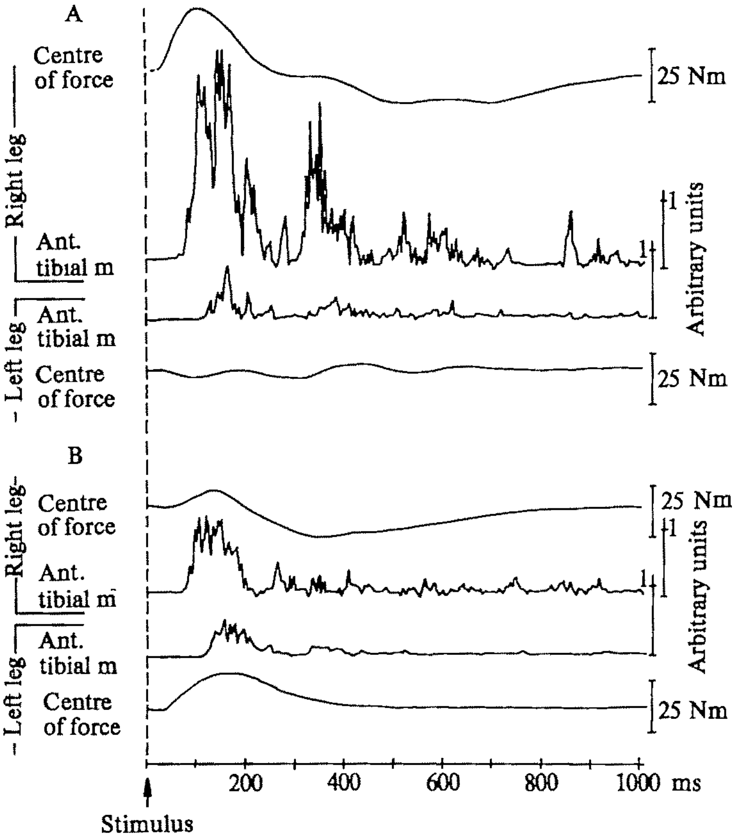

FIG. 3. Averaged (n = 10) responses of tibialis anterior muscle activity (*middle traces*) and platform force recordings of both sides after randomized supramaximal electrical stimulation of the right (A) and the left (B) tibial nerve in a patient with a left spastic hemiparesis.

these patients, neither after a displacement on the unaffected nor on the paretic side could a significant EMG response be distinguished on the paretic side, whereas TA responses were present after both manoeuvres on the unaffected side.

In 3 patients with longlasting spasticity, following stimulation of the spastic side, a clonus-like phenomenon was observed (clonus was never seen on the spastic side during spontaneous balancing movements). When the gastrocnemius EMG was recorded in such a patient (with a right spastic hemiparesis), the EMG activity was more synchronized than that on the unaffected side, occurring at a frequency of 4 to 5 Hz (*see* fig. 4). In addition, the TA as well as the GS response appeared earlier on the unaffected nondisplaced side. Whereas the EMG synchronization normally seen after displacement tended to become desynchronized during the oscillations following the displacement, synchronized EMG bursts appeared over a longer time period on the spastic side.

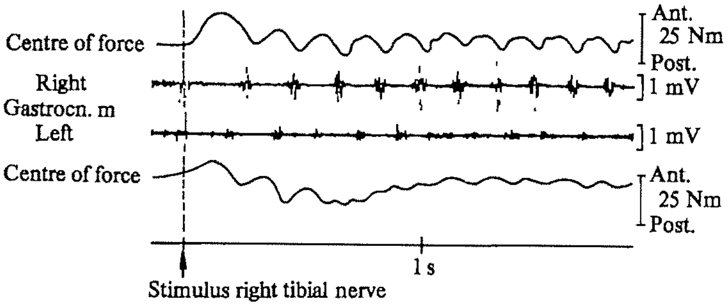

FIG. 4. EMG responses of gastrocnemius muscles and platform forces for both sides after supramaximal electrical stimulation of the right tibial nerve in a patient with a right spastic hemiparesis while standing on the two see-saws.

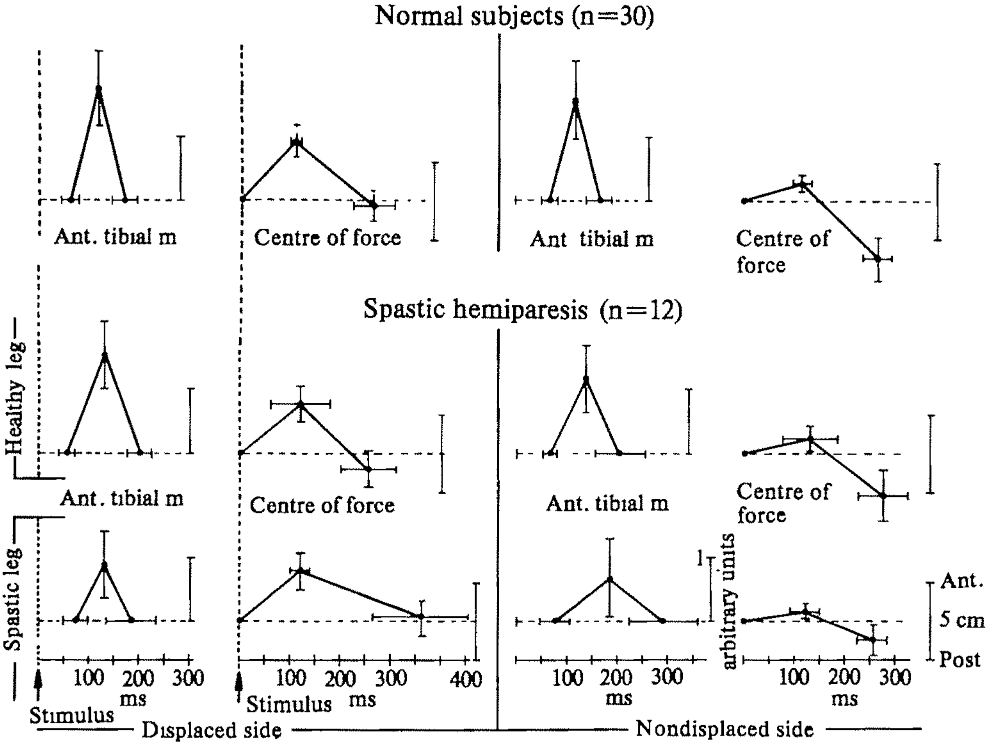

FIG. 5. Mean values (with SD) of the rectified and averaged (n = 10) tibialis anterior muscle responses and platform force recordings of both sides after unilateral electrical stimulation of the tibial nerve in 15 normal subjects (*top row*) and 12 patients with spastic hemiparesis (*bottom two rows*) while balancing on separate see-saws. The arrow indicates stimulus timing. One unit corresponds to about 1 mV.

The averaged histograms of 12 patients with spastic hemiparesis are shown in fig. 5. The mean latency between the displacement and the onset of TA activation on the unaffected leg was found to be 57 ± 13 ms, irrespective of which foot had been displaced. On the spastic side the mean latency was found to be 80 ± 19 ms when the spastic foot was displaced and 78 ± 11 ms when the unaffected one was displaced. The mean delay on the spastic side of all patients tested amounted to 22 ms, whether the spastic or the unaffected side was displaced. This difference in latency was significant ($t = 6.58$, $P < 0.01$).

In normal subjects the amplitude of the EMG response was the same on both the displaced and nondisplaced sides (fig. 5). On the spastic side of patients, however, the amplitude of the earliest phasic EMG component in TA in both conditions (displaced and nondisplaced) was reduced on average to about half the level of the EMG responses obtained on the unaffected side. The amplitude of the EMG responses on the unaffected side was also reduced (on average to about 80 per cent of normal) when the spastic leg was displaced (fig. 5). These differences in EMG amplitude between the unaffected and the spastic sides were significant, both for displacement of the unaffected foot ($t = 5.82$, $P < 0.01$) and the spastic foot ($t = 4.97$, $P < 0.02$). There was, however, no correlation between the onset latency and the reduction of EMG response on the spastic side.

Whereas the amplitude of the anterior displacement of the see-saw produced by a triceps surae contraction was the same on both sides, irrespective of which of the two legs was displaced, the compensatory balancing movements following the displacement were reduced in amplitude in the spastic leg (fig. 3). The damping of the oscillations that followed was even more obvious on the spastic side when the unaffected side was displaced, with a corresponding reduction in amplitude of EMG activity in TA (fig. 5). In contrast, there was only a little damping on the nonaffected leg when the spastic one was displaced, and only a slight reduction in the amplitude of TA EMG. The latter became apparent when oscillations of the nondisplaced side in healthy subjects were compared with those of the nondisplaced unaffected side in patients with spastic hemiparesis (fig. 5). It seems, therefore, that the mechanical damping of counterbalancing movements on both sides of patients with spastic hemiparesis was related to the amplitude of TA EMG responses. However, when the magnitudes of TA activation in the displaced and nondisplaced legs were correlated statistically with the amplitude of see-saw movement, there was no significant relationship between these two parameters. In addition to the reduction in amplitude, fig. 5 illustrates that the counterbalancing movement on the displaced spastic side was considerably slower than that of the unaffected side of patients, as well as that of healthy volunteers.

Patients with spastic paraparesis. In patients with spastic paraparesis, which in most cases was due to a chronic spinal lesion at a cervical level, the EMG responses following a unilateral displacement were delayed in their onset. Depending on the severity of paresis, they were also reduced in amplitude on both sides, with a longer onset delay on the more affected side. No basic differences in response were therefore observed from those of patients with hemiparesis. The larger mean amplitude of EMG responses corresponds with the fact that the spasticity was more evident in this group of patients, while paresis was of a minor degree.

Unilateral Tibial Nerve Stimulation During Stance on Solid Ground

Many patients (not listed in Methods) found it impossible to balance on the see-saws. Their compensatory movements following unilateral displacement induced by tibial nerve stimulation were thus tested only during stance on the two separate solid force-measuring platforms. Their EMG responses did not significantly differ from those obtained in the patients tested in both conditions. This seemed to be a valid comparison with similar tests on the see-saws because in healthy subjects quite similar bilateral EMG responses in TA were observed in both situations. However, the responses appeared at longer latencies (87±15 ms) as compared with those in the see-saw experiment (Dietz and Berger, 1982). In agreement with the see-saw experiments, the EMG responses obtained in the 12 patients examined in both conditions were later in onset on the spastic side with respect to the unaffected side and the healthy subjects, whether the tibial nerve of the spastic or the healthy side was stimulated. This is summarized in fig. 6.

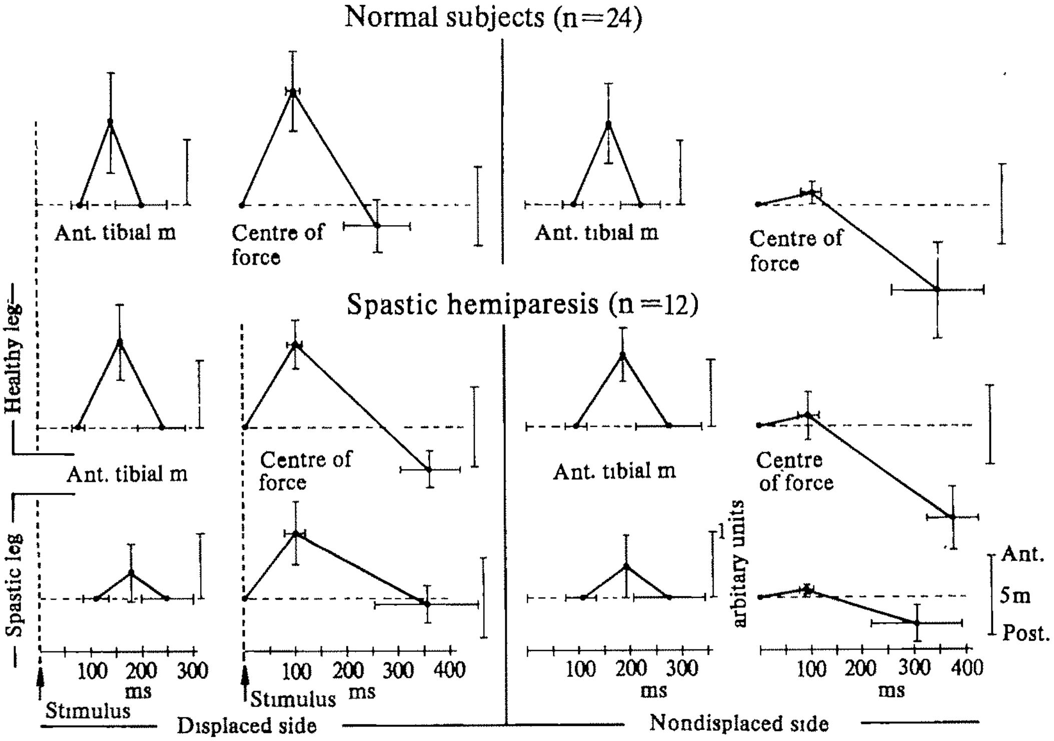

FIG 6. Summarizing histograms, as explained in fig. 5, obtained from 15 normal subjects (*top row*) and 12 patients with spastic hemiparesis (*bottom two rows*) standing on separate platforms

The mean latency calculated for all patients on their unaffected sides (displaced 85 ms ± 15, nondisplaced 89 ms ± 25) was significantly shorter ($t = 4.22$, $P < 0.01$) than on the spastic side (displaced and nondisplaced 117 ± 25 ms). The difference in latency between the two sides (30 ms) was therefore a little longer than that observed in the see-saw experiments (22 ms).

Other observations concerning the amplitude of EMG responses and the compensatory movements made during balancing were similar. Although the reduction of EMG response on the spastic side was less pronounced, it was still significantly smaller on the spastic side when the unaffected leg was displaced ($t = 4.56$, $P < 0.02$) as well as when the spastic leg was displaced ($t = 4.25$, $P < 0.01$). The anteroposterior force fluctuations following unilateral tibial nerve stimulation were damped on the spastic side regardless of which side was displaced ($t = 6.12$ and $t = 5.42$, respectively, $P < 0.01$). Similar results were obtained when the patients with spastic paraparesis were standing on the two solid force-measuring platforms, with delayed and reduced EMG responses on both sides.

When the tibial nerve was stimulated submaximally and no visible displacement was induced, in neither the healthy subjects nor in the patients did EMG responses appear. This fact, in combination with the appearance of the same EMG responses following a sudden see-saw displacement, suggests that the mechanical displacement of one foot is the stimulus required to evoke the compensatory EMG responses.

Mechanical Effect of Tibial Nerve Stimulation

In order to investigate to what extent the damped movements on the spastic side were due to the reduced EMG responses or to changes in the mechanical properties of muscle, the tibial nerve was stimulated supramaximally while the patient was sitting relaxed with the leg fixed. In fig. 7 the twitch contraction curves under isometric conditions of the triceps surae muscles of both legs are shown for a patient with spastic hemiparesis. While the peak tension of the twitches was the same for both sides, the contraction and relaxation time was delayed for the spastic side relative to the unaffected one. This was true for all 4 patients tested.

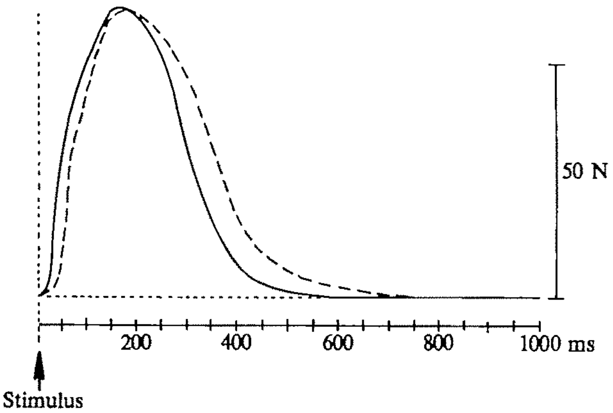

FIG. 7. Averaged ($n = 10$) isometric force output of triceps surae during stimulation of the tibial nerve on the spastic (interrupted line) and the unaffected leg (continuous line) of a patient with spastic hemiparesis.

DISCUSSION

Two main results arise from these experiments. First, in spastic hemiparesis and unexpected plantarflexion of the foot on the see-saw (by anterior tilt or tibial nerve stimulation), the TA response of the spastic leg was delayed (20 to 30 ms). The TA response of the unaffected leg appeared with a normal latency of about 55 ms. These results occurred whether the spastic or the unaffected leg was perturbed. This implies that the afferent pathway cannot be responsible for the delay on the spastic side. The severity of paresis did not influence the delay. Secondly, in spastic hemiparesis and paraparesis there was a reduction in the EMG response activity on the spastic side which was dependent on the severity of paresis. The question then arises as to how these results can be interpreted in terms of the spinal and supraspinal reflex contributions and in relation to the nervous structures affected by the motor disability.

Presumed Reflex Pathways

It has been argued that the bilateral appearance of EMG responses following a unilateral displacement and a latency of about 55 ms on both sides in healthy subjects makes it unlikely that these responses are mediated by monosynaptic reflexes (Dietz and Berger, 1982). Despite the exaggerated tendon jerks of the spastic side and the rather high stretch velocity applied to the TA by the displacement (200 to 250 deg/s; *see* Dietz and Berger, 1982), no sign of monosynaptic stretch reflex activity could be observed in the TA EMG responses.

Although the latency of 55 ms seems to be too short to constitute a transcortical reflex pathway, transmission through the brainstem cannot be excluded. For example, a TA reflex response has been obtained with a latency of 60 ms following tibial nerve stimulation in children with cerebral palsy, and this response was attributed to the spinobulbospinal reflex (Shimamura, 1973). This reflex was difficult to obtain in normal subjects (Shimamura *et al.*, 1964). In our experiments this reflex would be expected to appear on the spastic rather than on the unaffected side, but this was not the case.

In addition to the latency being compatible with polysynaptic spinal reflex transmission, there is some evidence arising from animal experiments which supports the idea that at least the early part of the EMG response is generated by propriospinal neurons. Such propriospinal neuronal circuits are known to be responsible for interlimb coordination and have been closely related to the locomotor generators (*see* Baldissera *et al.*, 1981, pp. 553 *et seq.*). According to these authors, the integrity of these spinal neuronal circuits depends on the influence of supraspinal motor centres. Therefore, in the normal state, the difference in latency observed between the postural reactions during stance on solid ground and unstable ground may be explained by a modulation of these spinal reflexes due to the intervention of vestibular control. It must be borne in mind, however, that the displacements occur more rapidly during stance on the see-saws, which could also explain the difference in latency.

This aside, it remains true that a depression of a variety of spinal polysynaptic actions takes place following decerebration in the cat (Baldissera *et al.*, 1981, pp. 564 *et seq.*), and that more 'primitive' reflex responses with longer delays then become dominant (Andén *et al.*, 1966). In this respect the observation that the early part of EMG response is lacking in spastic paresis would match well with the assumption of its spinal origin.

A similar depression of polysynaptic reflex responses was described in patients with supramotoneuronal lesions, who showed no early synchronized burst in the TA EMG recorded during electrical stimulation of the sole of the foot (Fisher *et al.*, 1979).

While a spinal origin for the early EMG component is indicated by the above arguments, the origin of the rest of the response must, to some extent, remain open to question. The fact that there was a strong correlation between the severity of paresis and the degree of reduction of the TA response, but that the level of paresis did not influence the delay, may support the view that an extraspinal mechanism is also involved. The latencies of 87 ms (during stance on the see-saws) and 117 ms (stance on solid ground) on the spastic side raise the possibility that long-loop reflexes contribute to this delayed EMG response. Thus the damping of the response on the spastic side could be due to the impairment of supraspinal mechanisms. If this is true, the minor reduction of the EMG response on the unaffected side, seen when the spastic foot was displaced, could be explained by an impairment of the ipsilateral uncrossed part of the descending pathway (*see* Evarts, 1966).

Interaction of Different Reflex Mechanisms

In a few patients the foot movements following a perturbation turned into a clonus of the spastic leg, which reflects the exaggerated monosynaptic stretch reflex activity of the GS muscle, although this does not contribute to the compensation of the perturbation. It seems, therefore, that in spasticity there exists an imbalance of reflex systems such that compensatory reactions mediated by polysynaptic reflexes are suppressed and monosynaptic stretch reflexes predominate. The latter are known to be ineffective during rapid movements (Gottlieb and Agarwal, 1979). A similar depression of the polysynaptic reflex component (the 'M2 response'), believed to represent a long loop reflex response, was observed during compensatory motor adjustments following perturbations applied by a torque motor to the arm muscles of spastic patients (Lee and Tatton, 1978).

The normal motor adjustments described here are obviously not identical with the contribution of the stretch reflex to the GS EMG previously described for running and hopping movements in healthy volunteers (Dietz *et al.*, 1979; Dietz and Noth, 1978) because the latter appeared earlier and was closely related to muscle stretch.

Our present results cannot indicate to what extent these motor adjustments are induced by muscle stretch. In recent experiments on gait perturbations, similar motor adjustments also appeared when the normally occurring muscle stretch was inhibited (Dietz *et al.*, 1984). The reflex responses might be induced by afferent input from several sources, such as joint and several muscle receptors. Skin receptors did not obviously play an important role, since anaesthesia of the foot did not alter the compensatory movements (unpublished observations).

Musculomechanical Factors

Beside the observation of a delayed response on the spastic side, damped oscillatory see-saw movements were seen during spontaneous balancing (as well as after displacement) and were associated with reduced and largely tonic activation of the leg muscles.

It is difficult to distinguish to what extent this phenomenon is due to changes and reduction in the neural activation of TA following a displacement or to alterations in the mechanical properties of muscle. These changed properties have been stressed as factors underlying muscle hypertonia in spasticity (Dietz, *et al.*, 1981; Dietz and Berger, 1983). The results obtained here tend to support the initial suggestion of reduced TA activation as the main factor responsible for the damped counterbalancing movements. However, the delay on the spastic side in the twitch contraction curves can be partly attributed to changes in the mechanical properties of muscle. The relative importance and degree of interaction of these two factors—neuronal muscle activation and mechanical properties—cannot be established from this study.

ACKNOWLEDGEMENTS

We thank Professor J. Noth for helpful comments on the paper. We are grateful to Mr Stuart Fellows for reading and correcting the final version and Mrs U. Rõmmelt and G. Horstmann for technical assistance.

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 70—Hirnforschung und Sinnesphysiologie and project Be 936/1-1).

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(*Received June 28, 1983. Revised February 7, 1984*)

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NOTICES OF RECENT PUBLICATIONS

Neuropsychology after Lashley. Edited by Jack Orbach. 1982. Pp. 541. London and Hillsdale, NJ: Lawrence Erlbaum. Price £19.95.

Karl Lashley was a neuropsychologist of outstanding distinction whose early studies of brain mechanisms and intelligence in the rat, and later the monkey, led him seriously to question traditional theories of cortical function with their strong emphasis on precise cerebral localization. Instead, he put forward two closely related principles which he termed equipotentiality and cortical mass action and which for a time won a considerable measure of acceptance. These principles came, however, to raise serious difficulties and by the time of Lashley's death in 1958, concepts of localization were once again in the ascendant. Nonetheless Lashley is still widely remembered as a leading experimental psychologist in his time and the virtual founder of contemporary neuropsychology.

In 1978, Jack Orbach, once a graduate student with Lashley and at present a professor at the City University of New York, decided to honour the semicentennial of the original publication of Lashley's celebrated monograph on *Brain Mechanisms and Intelligence*, easily the most influential of his earlier publications, by organizing a series of lectures on aspects of neuropsychology in his own university in which those invited to give lectures should be for the most part individuals who had known Lashley as friends, colleagues or graduate students. To these were added a few younger men who had not known Lashley personally, but whose work owed much to his inspiration and example. Almost all of those invited to deliver lectures agreed to do so and, subsequently, to write them up for publication under Orbach's editorship. A small number who were unable to deliver their lectures submitted manuscripts which the editor has included in this volume along with the rest.

Apart from the first five, which are largely devoted to biographical material concerning Lashley and his career, these essays have been chosen by their authors as representing their own work and interests, though many of them relate more or less directly to Lashley's own work and ideas. These essays vary appreciably in length, scope and content, and such common ground as they exhibit is largely limited to current lines of work and interpretation in neurophysiology and the behavioural sciences. Before commenting on them, however, it may be thought in place to say a word about the five introductory essays, all of which appear to have been prepared and written by Dr Orbach.

Although in no sense constituting a formal biography, these introductory essays throw a good deal of light on Lashley's career and personality, much of it due to a substantial memoir by Frank Beach, originally published as an obituary notice in the proceedings of the National Academy of Science. One may also mention a perceptive sketch by Sir Frederic Bartlett, condensed from a memoir published in the 1960 volume of Memoirs of Fellows of the Royal Society, of which Lashley was a Foreign Fellow. Another interesting sidelight, which we owe to Dr Orbach, is an extract from a correspondence between Lashley and Babkin, who was clearly in search of material for his biography of Pavlov. It is evident from Lashley's letter that, although a convinced behaviourist who had worked closely in his younger days with J. B. Watson, he had little respect for Pavlov's work and considered that theories based on reflexes and conditioned reflexes were becoming obstacles to our understanding of the functions of the cerebral cortex.

As regards the neuropsychological articles that together constitute the bulk of this book, it must be admitted that, excellent as many of them may be, they in no sense constitute a book with a coherent theme other than the somewhat tenuous link with Lashley. Nevertheless, most of them are well worth reading and bring out well the astonishing extent of change and development in the biological sciences since Lashley's death. This, one may suspect, has been due more to technical advance than to the discovery of fresh ideas, but even so, the advance in our understanding of important areas of neuropsychology is indeed encouraging.

Among individual contributions, the present reviewer was particularly interested in two papers on vision by Chow and Riesen, both stalwart Lashley men who have much to say about development, plasticity and deprivation in the visual system. These authors have done well in bringing their material up-to-date without losing the basic flavour of Lashley's thought. Other good papers deriving from Lashley are those of Doty on aspects of the visual system and on memory, and Weiskrantz with a splendid paper covering the neuropsychology both of memory and of amnesia in animals and man.

Although these, and several other, articles included in this volume lean heavily on neuropsychology and experimental psychology, clinical neurology is in no way excluded. This is particularly appropriate when it is borne in mind that although Lashley worked exclusively with animals, he gained much from neurologists such as Head and Klüver, who were primarily clinicians. It is encouraging that Weiskrantz has seen fit to combine human with primate studies and that Lindsley writes here on the neural mechanisms of arousal and attention and E. Roy John on the recovery of function after brain injury. We may likewise welcome Berman's article on sensory-motor interaction, with special reference to dorsal rhizotomy, and Diamond's on cortical architectonics.

The closing article in this book is by Roger Sperry who, somewhat predictably, writes on forebrain commissurotomy and conscious awareness. Sperry is certainly Lashley's most distinguished successor and it is difficult to suppose that the latter would not have found Sperry's split-brain work of outstanding interest. At the same time, Sperry's claim that subjective phenomena have a place and use in brain function, might have given difficulty to Lashley as a convinced behaviourist and well-known sceptic in matters of theory. Although one may believe that the interaction of body and mind is a difficult theory to sustain, it may nonetheless be true that Sperry has become closer than anyone else to achieving the coalescence of brain and mind that Lashley so earnestly sought.

O. L. Zangwill

Recent Advances in Epilepsy. Edited by Timothy A. Pedley and Brian S. Meldrum. 1983. Pp. 255. Edinburgh: Churchill Livingstone. Price £19.50 (soft cover).

Over the last few years there have been a number of small books, largely from the USA, dealing with epilepsy. Generally these have attempted a comprehensive coverage and generally they have had serious deficiencies. This new volume has a different format, and consists of 13 essays reviewing specialized areas of experimental and clinical work. I would quibble about the title, as the essays are essentially review articles, and in some, 'recent advances' are noticeably absent. This is a minor complaint, however, as the essays are of uniformly high standard and the work is well written, edited and produced. Outstanding amongst the contributions are the chapters on Violence and Epilepsy (Treiman and Delgado-Esqueta), Pharmacological Considerations in the Search for New Anticonvulsants (Meldrum), and Measurement of Saliva Drug Concentrations (Knott), and each of these is comprehensive and authoritative; here the distinction between original work and review is blurred. Also good are the chapters on Interictal Behaviour and Temporal Lobe Epilepsy (Trimble) and Infantile Spasms (Bellman), both of which cover their subjects admirably. Interesting, and really the only 'research paper', is that on Biorhythmic Modulation of Epileptic Events (Kellaway and Frost) which deals with the time relation of seizures. There are three chapters dealing with individual drugs (with thesaurian titles)—Phenytoin: an Update, Sodium Valproate: a Reappraisal, and Carbamazepine Re-examined. Each is well written, but by neccessity short, and the information is readily available elsewhere. All in all this excellent book, the first in a series, is a useful addition to the shelves of any neurological library.

Simon Shorvon

Peripheral Nerve Disorders (Neurology 4). Edited by Arthur K. Asbury and R. W. Gilliatt. 1984. Pp. 339. Sevenoaks, Kent: Butterworth. Price £25.00.

The purpose of Butterworths International Medical Reviews is to report on subjects in which 'recent progress has altered the way in which patients are managed'. It follows the format of its successful forerunner, Modern Trends. In this issue, edited by A. K. Asbury and R. W. Gilliatt, the subjects reviewed include aspects of acute and chronic polyneuropathy, assessment and management of autonomic disorders, geographical patterns of neuropathy in India, Japan, and Africa, and neuropathies associated with systemic disease, with diabetes mellitus, with connective tissue disorders, with toxins, with inherited metabolic disorders, and with exogenous compression and entrapment. The editors appear to have been of two minds, the one to produce a short textbook on peripheral neuropathy, and the other to compile a series of in-depth medical reviews of subjects related to peripheral neuropathy. Irrespective of intent, this book, 300 and some pages long, does provide aspects of both and in a very readable form. To illustrate what may be found in the book, a few examples will be provided. The chapter on diagnosis and management of acute paralysis by A. Ropper and B. Shahani emphasizes clinical and electrophysiological diagnosis, management of respirator-bound patients and comparison of plasmapheresis and conventional care in the Guillain-Barré syndrome. Patients on plasmapheresis were on the ventilator and in intensive care for fewer days, and left the hospital sooner, than did those on conventional care. The authors state that larger trials are needed but take the unexpected position of suggesting that if the multicentre trial does not show a beneficial effect, 'then the same problems that plagued the interpretation of steroid trials may pertain'. They seem to be saying that they will accept the results of the study if it is positive, but not if it is negative—hardly an open attitude! Possibly what is really needed is a double-blind trial using plasmapheresis and sham plasmapheresis! M. Brown and D. Greene provide a succinct, yet detailed, account of possible metabolic and cellular alterations which may relate to the development of neuropathy in diabetes mellitus. Harding and Thomas emphasize that linkage studies have shown that peroneal muscular atrophies are heterogenous and that the locus for HMSN-I is near the Duffy locus on the long arm of chromosome 1. The chapter by R. W. Gilliatt and M. J. G. Harrison on nerve compression and entrapment provides evidence that these workers have not only made important fundamental contributions, but have applied these insights to the human entrapments—possibly the commonest of all neuropathies. Overall, this is a worthwhile book which can be recommended.

P. J. DYCK

Entrapment Neuropathies. By David M. Dawson, Mark Hallett and Lewis H. Millender. 1983. Pp. 307. Boston: Little, Brown. Price $38.50.

It is a pleasure to welcome this monograph on entrapment neuropathy which is, I believe, the first English language book devoted to this subject since Kopell and Thompson's monograph published in 1963.

It is the result of close collaboration between physician and surgeon, and it provides an admirably lucid and balanced account of entrapment syndromes. There are many excellent and previously unpublished photographs of lesions seen at operation. Quite rightly the common syndromes receive the most extensive coverage; indeed about half the book is devoted to median and ulnar entrapment but, in addition, rare syndromes such as suprascapular or ilioinguinal entrapment are also discussed. There are additional chapters on pathological mechanisms and on electrophysiological techniques.

The book is a valuable addition to the literature of peripheral neuropathy, and can be strongly recommended.

R. W. GILLIATT

Disorders of Peripheral Nerves. By Herbert H. Schaumburg, Peter S. Spencer and P. K. Thomas. 1983. Pp. 248. Philadelphia: F. A. Davis. Price $47.50.

These 250 pages were originally derived from a course for students. It owes much to this fact, including its clear and very didactic structure and easily readable style. In the first chapter the anatomical and histological features of peripheral nerves are described. Perhaps it would also be useful to remind the reader of the electrophysiological bases of peripheral nerve activity? In the second part, the principles of subdivision of peripheral nerve diseases in two categories are listed. Finally a chapter is dedicated to each one of the main aetiological groups of neuropathies: the inflammatory neuropathies, diabetic neuropathy, neuropathy in alcoholism, nutritional deficiencies and malabsorption, uraemic neuropathies, the porphyrias, endocrine neuropathies, hereditary disorders of lipid metabolism with neuropathy, hereditary motor and sensory neuropathies, toxic neuropathies due to pharmaceutical agents, to occupational, biological and environmental agents, neuropathies associated with malignancy and dysproteinaemia, amyloid neuropathy, ischaemic neuropathy, infectious and granulomatous neuropathies and cryptogenic neuropathies. Lesions due to mechanical factors are subdivided into those of acute traumatic origin and the chronic compression neuropathies. A final chapter briefly describes the indications and techniques for the electrophysiological and biopsy examination of peripheral nerve disorders. Every chapter is followed by an up-to-date list of references. The chapters on lesions of single peripheral nerves are illustrated by the well-known figures of Haymaker and Woodhall.

The most important characteristics of the different aetiological groups are well described in a concise way. They do not just expose the clinical aspects to permit a diagnosis, but also give an excellent insight into the pathogenetic mechanisms. If this book is compared with the standard work on peripheral nerve diseases which has just appeared in the second edition (*Peripheral Neuropathy*. Edited by P. J. Dyck, P. K. Thomas, E. H. Lambert and R. Bunge. Second edition. 1984. Philadelphia: W. B. Saunders), the particular merit of the present volume becomes evident: it synthesizes the essentials of peripheral nerve diseases, accepting some simplifications but presenting all that is needed for the practical purpose of making a diagnosis and understanding the principles of the pathology of peripheral nerves.

This excellent book is aimed at interns and residents in hospitals, but also practising neurologists and nonspecialists. Here one can rapidly read up the single disease entities, but the references also permit a more detailed study of the subject. The thoroughly compiled index makes access easy.

MARK MUMENTHALER

Management of Head Injuries. By Bryan Jennett and Graham Teasdale. 1981. Pp. 360. Philadelphia: F. A Davis. Price: Cloth £40.65. Paperback (1983) £22.35.

First published in 1981, this book is already regarded as a major contribution to the care of head-injured patients. The reduction in price accompanying the new paperback edition must only serve to increase its popularity.

The authors draw mainly from individual experience based on the extensive multidisciplinary head injury research programme at the Glasgow neurosurgical unit and from the wealth of information available in the head injury data bank, collating information from two other large centres in Rotterdam and Los Angeles as well as their own. Head injury 'management' is described in its broadest sense with introductory chapters on epidemiology and pathology followed by a detailed description of patient assessment. Care of the head-injured patient ranges from basic principles at the scene of the accident to operative techniques. Valuable information is included on the residual effects of both minor and severe head injury and on relevant prognostic features.

The authors' critical approach to the many different aspects of head injury management, and honesty in admitting deficiencies in present knowledge, is refreshing. Ambiguity is absent and terms are clearly defined; the layout and clarity of the text makes easy reading. Illustrations are clear, although a few, such as the diagram showing the benefits of airway insertion, seem superfluous. This book will undoubtedly provide invaluable and long-lasting guidance to all involved in head injury management whether in the accident and emergency department, the primary care ward or the neurosurgical unit.

K. W. LINDSAY

Surgical Management of Cerebrovascular Disease. By R. G. Ojemann and R M. Crowell. 1983. Pp. 316. London and Baltimore: Williams and Wilkins. Price £52.00.

The last two decades have seen remarkable advances in the surgery of cerebrovascular disease, especially for intracranial operations where the whole nature of the work has been transformed by the development of the operating microscope and appropriate micro-instrumentation. Procedures which only twenty years ago were regarded as virtually impossible, such as the clipping of vertebrobasilar aneurysms or the total excision of basal or deep-seated angiomas, have become part of the established repertoire of every major neurosurgical service. It now seems likely that the pace of advance is beginning to slow down, at any rate so far as the purely technical aspects of surgery are concerned. The time may be ripe for a concise survey of the whole field from the point of view of the practical operating neurosurgeon.

This superb book, written by two eminent American neurosurgeons, can hardly be faulted. Just about every aspect of the surgery of cerebrovascular disease is fully covered, from surgery of the extracranial arteries, to microvascular intracranial anastomoses. The text is clear, succinct and to the point. A detached and fair attitude is maintained in discussing matters of controversy. The fact that the book is written by just two surgeons means that the tedious repetition which afflicts multiauthor books has been avoided. References are well chosen, relevant and up to date. The standard of the numerous line and radiological illustrations is excellent as are the typography and general production of the book. This reviewer's only criticism is that discussion of the results of different procedures tends to be confined to cases treated by the authors rather than being an assessment of what is generally obtained. This is perhaps becoming a general fault in neurosurgical texts, especially in those emanating from North America. Results achieved by a handful of outstanding neurosurgeons of international reputation may well give rather too optimistic an impression of what is being generally achieved. However, this is a relatively minor criticism. It may be said with confidence that this book will be of value to all neurosurgeons, both those in training and those in established practice. It goes without saying that the libraries of neuroscience units should purchase it. Its price may seem high but it is by no means unreasonable in view of what these authors have given us.

R. S. MAURICE-WILLIAMS

Handbook of Psychopharmacology. Volume 15. **New Techniques in Psychopharmacology.** Edited by L. L. Iversen, S. D. Iversen and S. H. Snyder. 1982. Pp. 425. New York: Plenum Press. Price $55.00.

Research covered by the *Handbook of Psychopharmacology* extends from basic enzymatic studies, through structure-activity relationships and neurotransmitter topography, to ethology, operant behavioural technology and theories of monoamine disturbance in psychiatric disease. The range of interest of the editors and their capacity to engage the enthusiasm of a wide spectrum of contributors is not yet exhausted. The current volume is the first of Section IV on Basic Neuropharmacology: an Update. Of the 8 chapters 3 are concerned with techniques of measurement (electrochemical detection, radioreceptor assays and high performance liquid chromatography) two with neurotoxic lesioning (with capsaicin and excitatory amino acids), two are relevant to neuroanatomical issues (autoradiography and ^{11}C-deoxyglucose mapping) and a single chapter is devoted to intracellular recordings in brain slices.

As previous volumes have led us to expect, the standard of criticism and comprehensiveness is high. For example the chapter by R. N. Adams and C. A. Marsden on electrochemical detection provides an exhaustive account of the principles, development and problems of electrochemical detection in its applications *in vitro* for assaying monoamines and their metabolites, and *in vivo* for relating changes in these measures to behaviour and the effects of drugs. The chapter by S. J. Enna on radioreceptor assays provides a useful update on the versatility of these methods, although their exceptional utility in post-mortem brain studies perhaps deserves particular emphasis, and the contribution of H. R. Morris and G. W. Taylor on the application of HPLC techniques to the purification and characterization of neuropeptides, including some examples of their early application to clinical material, is a model of lucidity. These chapters are readily accessible to the nonexpert as well as presenting an overview of present usage and problems for those who are already knee-deep.

Current interest in the use and mechanisms of action of neurotoxins is exemplified by chapters on capsaicin (appropriately, in view of its Hungarian origin, by Nagy) and the excitatory amino acid toxins (by Coyle). Nagy draws attention to the difficulties which remain in understanding the sensory-excitatory and neurotoxic actions in the neonate and the adult of this curious substance, and in interpreting in functional terms the specific deficits of pain and temperature appreciation which follow its experimental administration. The difficulties are greater than is often thought but the substance retains its unique interest. The growing body of work on the excitotoxins such as kainate, quisqualic acid and ibotenic acid, which in some ways are better understood, is ably reviewed by Coyle with particular emphasis on their selectivity for cell bodies.

Receptor autoradiography and the ^{11}C-deoxy glucose technique are covered by Kuhar and McCulloch, respectively. Both techniques promise a great deal, not least in implications for *in vivo* studies in man. Particularly intriguing are the studies of the effects of adrenergic agents on glucose utilization by the locus coeruleus system. The combined use of pharmacological and metabolic probes has great potential.

In the solitary chapter on electrophysiology, John Kelly expounds the virtues of the hippocampal tissue slice for intracellular recordings. He believes the technique yields information on ion channel opening times which will allow much closer correlations of physiological and biochemical data on relative potencies of action of drugs and will lead to a clearer understanding of their physiological mechanisms of action.

Overall the volume maintains the high standards of its predecessors. Few will read it from cover to cover, but many will be pleased to have access to a wealth of information in one place on this selection of techniques of growing importance.

T. J. Crow

The Chemistry of Behavior. A Molecular Approach to Neuronal Plasticity. By S. Reinis and J. M. Goldman. 1982. Pp. 602. New York: Plenum. Price $55.00.

This interesting volume reviews work relevant to plasticity and learning. It is unusual in its length (600 pages) and economy of authorship (2) as well as the breadth of its coverage, which almost qualifies it to be described as a compendium. The coverage is so wide that the reader is first tempted to conclude that much is irrelevant. Yet this view is difficult to sustain since the topic—the organism's capacity for adaptation in the face of a changing environment—is really the *raison d'être* of the brain; almost any aspect of brain function must be relevant to this issue.

The book reviews many basic subjects, for example the structure of membranes, the role of membrane lipids, the function of ion pumps and synaptic junctions, which might be regarded as basic neurophysiological background, but draws attention to their possible relevance to the mechanisms of learning. Other phenomena such as posttetanic potentiation, the association between brain structure and environmental changes (e.g. the work of Rosenzweig, Bennett and others), the acetylation of histones and nucleic acid changes in the course of learning (which have been thought by some to be directly related to the mechanisms of learning, are dealt with in more detail. So also is evidence for new protein synthesis in learning, and changes in protein phosphorylation and axonal transport. Theories that some specific neurotransmitters (e.g. acetylcholine and noradrenaline) are more directly involved than others in the mechanisms of neuronal plasticity are discussed, as also are questions of the neurophysiological and neurochemical bases of motivation. In each case a scholarly and balanced view of the recent literature is attempted.

The problem comes in drawing it all together. The answer has to be that we do not yet have incisive generalizations concerning the mechanisms of learning or, if we do, they are not generally accepted. There are interesting experimental phenomena and much potentially relevant basic knowledge but no framework that can be relied upon. One thought that occurred to this reviewer was that, comprehensive though in some respects this book is, there are still gaps, and these are in areas that may be crucial. For example, on p. 580 we read 'A critical examination of the literature on the role of various brain areas in learning is beyond the scope of this book' and yet it may be that the neuroanatomical problems are the ones that need to be solved first. There are indications of a rapprochement between clinical observations on the amnesic states and the findings of experiments on the effects of lesions on learning in animals. If one holds the view, contrary to Lashley, that there are certain structures (e.g. according to the current reviewer, the coerulocortical noradrenergic projection) that play a critical role in the mechanisms of learning, one may hope tó identify areas in the brain where specific neuronal interactions lead to the synaptic modifications underlying learning. The chemical and physiological features which distinguish these particular interactions from others will be those which are critical for plasticity.

Some problems in the field are illustrated in the final chapter when the authors set and attempt to answer three questions. (1) What are the chemical changes within an individual neuron which define an engram? Three different types of modification in nine different modes of intercellular communication are listed. (2) Where is the engram? Short-term memory is attributed to the hippocampus 'or elsewhere' but long-term storage 'has no such limitations'. (3) How is the engram organized, stored and retrieved? Hebb's cell assemblies, John's hyperneurons and Bindra's pexgos are mentioned but there is no account of how they answer this question. On the difficult but central problem of the neuronal mechanisms of learning Reinis and Goldman have formulated some questions and reviewed much relevant recent work, particularly neurochemical, but have not given new answers.

T. J. CROW

Cerebral Computed Tomography. A Text-atlas. By L. Weisberg, C. Nice and M Katz. Second edition. 1984. Pp. 356 Philadelphia: W. B. Saunders. Price £48.00

This is the second edition of a book originally published in 1978. Since then, knowledge about computed tomography has increased considerably, and the authors have responded by extensive revision of the text, bibliography and illustrations, most of the latter being of high quality.

The rather curious description 'text-atlas' is quite appropriate, since, although copiously illustrated, the text, if rather modest in scope, is the major part of the book. As befits a work whose senior author is a neurologist well versed in computed tomography, the chapters are clinically orientated, covering such subjects as neurological deficit of acute onset, head and face pain, etc., without undue overlap between the chapters. British practitioners may find it noteworthy that several paragraphs on brain death conclude the chapter on 'neurobehavioural syndromes'; at least they are left to the end! As I remarked recently in these pages in reviewing a similar publication, a chapter on the physical principles of computed tomography is surely out of place today as part of such a clinically orientated text.

Inevitably, to cover the whole of cranial, cerebral and orbital disease in 300 pages, most of which bear less than 50 per cent of text, leads to an abbreviated, shorthand style, so that many statements are misleading because of their terseness, while not strictly incorrect. Aggravating this fault is a tendency not to distinguish between what is known and what has been said or even merely suggested; even in a modest text, this should be made clear.

The book is generally well written, with only minor evidence of the transatlantic love of the grandiose: 'utilize' is always preferred as a synonym for 'use', and the short last chapter, on the effects of treatment, carries the title 'Evaluation of treatment modalities'. In the first edition there were long tracts of unbroken text, but the introduction of various orders of subheading has relieved the monotony and made specific subjects easier to locate. Also new are a number of useful tables. The page format is still unattractive, particularly for a book of this price, but clearly that does not detract significantly from its didactic value. I think it is too simple for specialist neuroradiologists, but other clinicians, general radiologists and those in training will, I am sure, find it a useful basic text.

IVAN MOSELEY

Handbook of Physiology. Section 10. **Skeletal Muscle.** Edited by Lee D. Peachey. 1983. Pp. 688. Baltimore: Williams and Wilkins for the American Physiological Society. No price given.

This substantial volume is a recent addition to the distinguished series of Handbooks published by the American Physiological Society which have as their central purpose the presentation of an integrated view of the history, recent research, present state and possible future of several aspects of specified fields of physiology. In this volume, the chapters cover a wide range relating to the structure, contraction, excitation-contraction coupling, specialization, adaptation and disease of skeletal muscle. The chapters have been prepared by authorities in these fields and are directed towards an audience of physiologists who desire a working knowledge of these topics and a basis for planning and executing research projects. The book will constitute a valuable, authoritative and up-to-date review for teachers and students in advanced courses in physiology. It will furnish a way into the extensive literature on muscle but, by its analytical approach, also provide a means of interpreting trends of development in these fields, thus giving the reader more perspective than is usually obtained by reading individual scientific articles.

Muscle has, because of its contractile nature and distinctive structure, stimulated the curiosity of generations of scientists. At each stage, the interest has been accelerated by the availability of new techniques. This acceleration has been more pronounced in the last twenty-five years because of the availability of several new techniques for studying the metabolism, structure and contractile properties of muscle. The early chapters on muscle structure show, by a wide range of transmission and scanning electron micrographs, the gross cellular morphology and microscopic features of the membranes and contractile mechanism of muscle. In a tissue in which the relations between structure and function are so closely linked, the exciting parallel development of techniques which have elucidated structure and enabled function to be explored becomes evident as the vision of the sarcotubular system in muscle and its function in excitation-contraction coupling becomes unfolded. The specialization to the particular tasks that the muscle has to undertake is a beautiful example of cellular specialization revealed by electron microscopy. Application of immunological methods to characterize individual proteins in skeletal muscle further elucidates this specialization.

The mechanism by which force is generated in skeletal muscle has long been an enigma, but the accumulating evidence for the sliding filament theory and the way in which cross-bridges are capable of generating force, has been explored by x-ray diffraction methods, and by studies of contractile properties in relation to ultrastructure and protein chemistry. Muscle is a biological machine for exchanging energy and doing work, and the energetics in muscular contraction have been extensively explored by a variety of techniques, including heat measurements, chemical analysis and nuclear magnetic resonance spectroscopy.

The crucial electrical properties of skeletal muscle membranes are analysed according to present membrane theories and what is known of ionic currents. The critical link between membrane excitation and the activation of chemical reactions by the release of calcium in muscle is one which depends much on the electrical properties of surface and tubular membranes, as well as on the extent and geometry of the tubular system. Visualization of the process of calcium activation by fluorescent dyes has greatly helped the elucidation of critical steps in the chain of events which leads from excitation of the surface membrane of muscle to activation of the contractile mechanism and exchange of energy from local chemical stores. These critical steps appear to be sensitive to various drug-related influences and the use of pharmacological studies has further extended the range of approaches available for study of these mechanisms.

The specialized muscles of insects and a wide range of other animal species provide examples which help explore the special adaptations of the common cellular machinery of muscles to different anatomical and functional needs. Further 'experiments of Nature' are provided from considerations of growth changes, the effects of exercise and alterations in environmental temperature in several animal species, ranging from tadpoles to man. From this impressive assembly of factual information the clear message emerges that muscle is a very adaptable tissue with alterations in structure, chemistry and contractile properties related to functional requirements and, further, that such changes are mediated by neurogenic, mechanical and humoral influences. These adaptations include not only changes within the muscle cell itself, but also in the supporting connective tissue and capillary bed.

The final section includes a review of the abnormal physiological mechanisms evident in diseases of skeletal muscle, as they are encountered in man and some animal models. The importance of such abnormal physiological processes, not only for diagnosis but as further examples of 'Nature's experiments', is that they can yield clues concerning normal human muscle function. Since the discovery of the first enzyme defect in human myopathy only three decades ago, it has been evident that there are probably many such defects which, in various ways, affect skeletal muscle. The number appears to be increasing year by year. Many are more of scientific interest than of any practical or therapeutic importance, but it is as well that they are recognized in order that the common symptoms of pain, fatigue or cramp should not be unjustly attributed to psychological causes, as has tended to happen.

The diagnosis of muscle disease is becoming progressively more practical with the advantages offered by needle biopsy for histochemistry or chemical analysis, and by new electrophysiological or mechanical measurements. Here again, topical nuclear magnetic resonance allows the opportunity for measuring muscle chemistry noninvasively at rest or during contraction, although its diagnostic value is as yet uncertain.

This great volume will undoubtedly become a classic in the extensive literature on skeletal muscle physiology, as indeed have the previous volumes in other fields in the *Handbooks of Physiology* published by the American Physiological Society.

R. H. T. EDWARDS

Schriftenreihe Neurologie. Band 25. **Comparative Neuropathology of Chronic Experimental Allergic Encephalomyelitis and Multiple Sclerosis.** By Hans Lassmann. 1983. Pp. 135. Berlin: Springer. Price DM 68.00.

This beautifully illustrated monograph examines the hypothesis that the chronic relapsing form of experimental allergic encephalomyelitis (EAE) provides a satisfactory model for multiple sclerosis (MS). The evidence depends largely on the histological resemblance of these conditions. Clinicians interested in the pathogenesis of MS will find the similarities and differences lucidly explained and clearly depicted. Acute ordinary EAE elicited with nervous tissue or myelin basic protein is an acute monophasic encephalomyelitis with little demyelination. However, the chronic relapsing form elicited in rats or guinea pigs, but most reproducibly in guinea pigs of one particular inbred strain (13), is characterized by the development of large demyelinated plaques with eventual gliosis which bear comparison with chronic MS. The author refers more briefly to the spectrum of human demyelinating disease through acute perivenous leukoencephalitis, and acute and chronic MS, regarding published cases of postrabies vaccine encephalomyelitis and one case of inadvertent human EAE as resembling acute MS. The burden of the monograph is that the essential histological features of MS are reproduced by one or other form of EAE. These include initial perivenous inflammatory cell infiltration, increased vascular permeability, demyelination, remyelination and gliosis. The fate of the oligodendrocytes in EAE and MS plaques is difficult to ascertain since conclusive electron microscopic identification of oligodendrocytes depends on the demonstration of processes in continuity with myelin lamellae which are lost, by definition, in demyelinated lesions. In the active lesions of chronic EAE, Lassmann depicts both intact oligodendrocytes and cells resembling oligodendrocytes which are degenerating, concluding that such damage is incidental to the main attack on myelin. The material from MS brains is relatively poorly fixed. Lassmann avoids depicting 'oligodendrocytes' therein but he does discuss the controversial issue of what happens to the oligodendrocytes in acute lesions, favouring the interpretation that these cells survive at least in the early stages of plaque formation. This issue deserves further examination as immunohistochemical techniques for identifying oligodendrocytes improve.

Clinicians and societies sponsoring research into multiple sclerosis could provide a real service by making autopsy material available for study as soon after death as possible to resolve this and other issues. Surprisingly good fixation can be achieved if central nervous system material is properly dissected and fixed in glutaraldehyde for electron microscopy. Snap frozen material may be needed for immunohistochemical staining of cell membrane antigens but as techniques improve paraffin and even plastic embedded sections are being used.

The inconclusive literature concerning fluctuations of blood, CSF and brain lymphocyte subpopulations in EAE and MS is ignored. The elusive nature of the antigen(s) causing chronic relapsing EAE is briefly discussed but the central issue of what precipitates the autoimmune state in MS is not addressed and chronic virological models of demyelinating disease are not compared with EAE. Discussion of these subjects would admittedly be speculative at present but this monograph does provide a solid basis of neuropathological fact on which the present and future generations of research into demyelinating disease will depend.

R. A. C. HUGHES

ISSN 0006-8950

Rec.
23.5.85

Brain

A JOURNAL OF NEUROLOGY

VOLUME 107 · PART IV · DECEMBER 1984

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Brain (1984), **107**, 989–1017

A NEUROLOGICAL BASIS FOR VISUAL DISCOMFORT

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SUMMARY

Certain patterns of stripes are judged to be unpleasant to look at. They induce illusions of colour, shape and motion that are sometimes perceived predominantly to one side of fixation. People who suffer frequent headaches tend to report more illusions, and if the pain consistently occurs on the same side of the head the illusions tend to be lateralized. The parameters of the patterns that induce illusions (including their shape, spatial frequency, duty cycle, contrast and cortical representation) closely resemble those that elicit epileptiform electroencephalographic abnormalities in patients with photosensitive epilepsy. The viewing conditions under which such abnormalities are likely to appear are also those under which more illusions are seen.

INTRODUCTION

Certain patients with epilepsy are photosensitive and suffer seizures induced by flickering lights and patterns of striped lines. When they are exposed to visual stimuli of this kind, epileptiform EEG activity (i.e., a photoconvulsive response) may be induced. The spatial and temporal characteristics of stimuli that induce epileptiform activity are surprisingly specific and have been reviewed elsewhere (Wilkins *et al.*, 1980; Meldrum and Wilkins, 1984). It can be inferred from the topography of the EEG activity and the nature of the stimuli that induce it that the paroxysmal discharge is triggered when normal physiological excitation in the visual cortex exceeds a critical level (Meldrum and Wilkins, 1984).

When people *without* epilepsy are asked to look at patterns of striped lines (such as that reproduced in fig. 1) they may report visual illusions of colour, shape and motion. These illusions have received extensive study over the last 100 years, but for the most part their origin remains obscure. It has been postulated that small eye movements are responsible for some of the illusions of motion, and some of the effects observed in patterns of concentric annuli have been attributed to fluctuations in the power of the lens of the eye (Campbell and Robson, 1958; Wade 1977). The techniques that have been used to differentiate between these peripheral ocular factors are often insufficient to exclude more central mechanisms. For example, after-images have been used to eliminate the contributions from eye movements, and an artificial pupil used to reduce the effects of fluctuations in accommodation, but both techniques involve a reduction in retinal stimulation. Although peripheral factors may play an important role in the generation of some of the illusions (Campbell and Robson, 1958), anomalous effects remain under conditions of stabilized vision and when fluctuations in accommodation can be discounted (Wade 1977). It has been argued (Georgeson, 1976, 1980; Welpe, 1976) that some of the illusions of shape derive not from peripheral factors but from inhibitory interactions

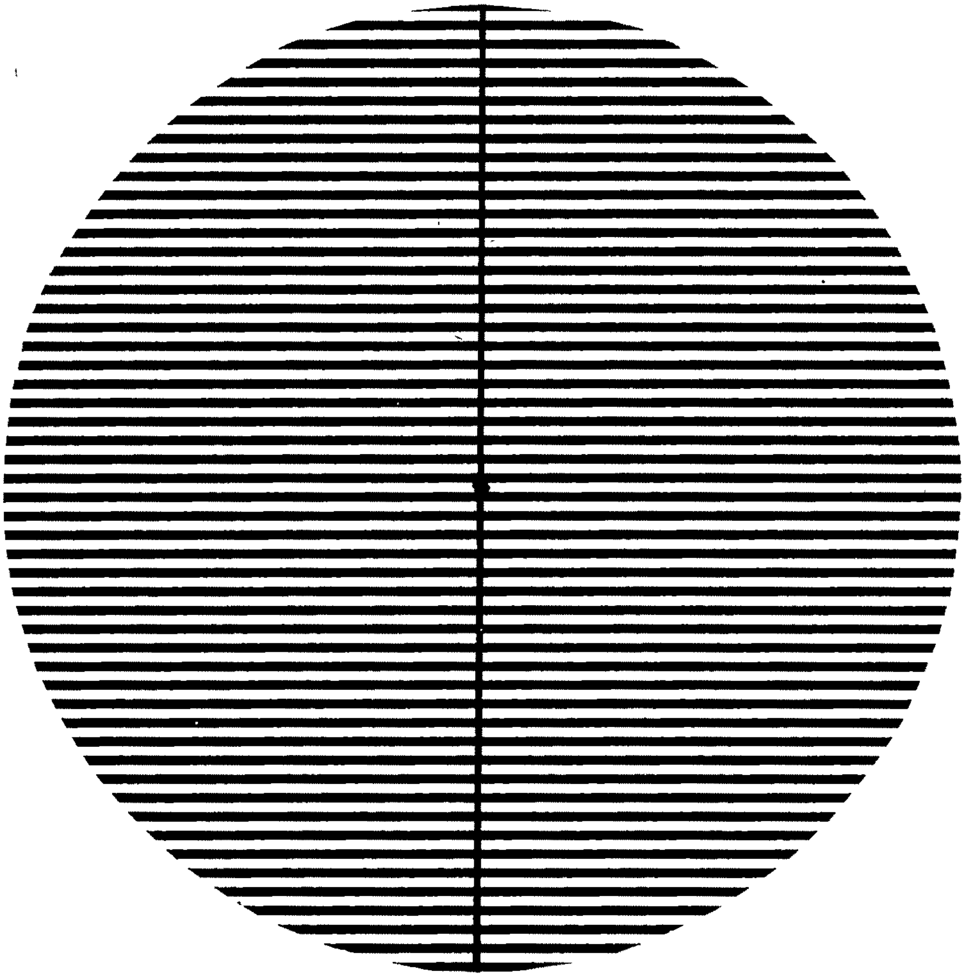


FIG. 1 A grating with square-wave luminance profile and a Michelson contrast of about 0.7. At a viewing distance of 43 cm this grating has a spatial frequency of 3 cycles/deg.

at the level of the striate cortex. It is possible that similar mechanisms also underly the illusions of colour and motion, particularly since the latter illusions are often integrated with those of shape in a unitary percept.

The wide variety of visual illusions seen in striped patterns have provided the impetus for the op art movement (Wade, 1978, 1982), and the paintings that have attracted most attention are those which generate spatial distortion associated with a subjective impression of movement. These effects can be unpleasant. Critics have described op paintings as 'assaulting the retina' (Oster, 1965). When Bridget Riley held an exhibition of her paintings the attendants complained of headaches and applied for dark glasses (*Daily Telegraph*, 1971). Complaints of this kind are not restricted to works of art. When escalators with a striped metal tread were introduced in the London underground there was criticism of the 'dazzling glare' that they produced (Collins, 1969). We know of no studies that have attempted to document the spatial properties of patterns that induce these unpleasant effects. One purpose of the present paper is to show that the spatial properties are quite specific and are related to the induction of visual illusions, headache and seizures.

The paper is divided into two sections. In the first section it is shown that the unpleasantness of patterns depends on their spatial frequency. The patterns that are maximally unpleasant are those that induce the most illusions. The number and location of the illusions that people report are associated with the incidence and nature of the headaches they suffer. In the second section it is shown that the visual stimuli that induce illusions and the conditions in which they do so are precisely those that in photosensitive patients induce epileptiform electroencephalographic abnormalities.

SECTION 1

'Pleasantness' of Patterns

In the first experiment subjects were asked simply to judge the 'pleasantness' of gratings with different spatial frequencies. Far from finding such a task incongruous, subjects took it seriously and gave very consistent judgements.

Experiment 1

The preference for striped patterns was measured using ratings of individual patterns, and paired comparison of pairs of patterns. Prints of vertical stripes (square-wave gratings with spatial frequencies of 0.5, 1.0, 2.0, 4.0, 8.0, 16.0 and 32.0 cycles/cm) were illuminated by a 100 Hz fluorescent source and presented at a viewing distance of about 50 cm for about 10 s each. The patterns were circular in outline, radius 100 mm, and they had a Michelson contrast of 0.7 and a mean luminance of about 100 cd/m^2. Twenty-nine female volunteers on the subject panel of the Applied Psychology Unit aged 19 to 68 years were tested as a group. Subjects with epilepsy were instructed not to participate. The subjects gave a preference for each of the 21 pairwise combinations of the seven gratings. Fifteen subjects received the pairs in random orders, and a further 8 received the pairs with a spatial frequency of less than 4 cycles/cm first (selected at random) and a further 6 received the pairs with frequencies above 4 cycles/cm first. In both the latter groups the pairs with mixed (high and low) spatial frequencies were given last. The pairs of gratings were presented one above the other, on the pages of a booklet. Each of the patterns was then presented individually in (different) random orders. Subjects were required (1) to rate the pattern for pleasantness on a five-point scale ranging from 'very pleasant' to 'very unpleasant' and (2) to list any visual or nonvisual effects that the pattern produced.

Results. The mean preference for each grating derived from the pairwise comparisons is shown in fig. 2A. It can be seen that gratings with more extreme spatial frequencies were preferred to those with frequencies between 2 and 8 cycles/deg. Using the method of circular triads (David, 1963, p. 25) the preferences are all significantly different from chance ($P < 0.01$). A comparison of the three curves provides an indication of the range effects (Poulton, 1979) introduced by the

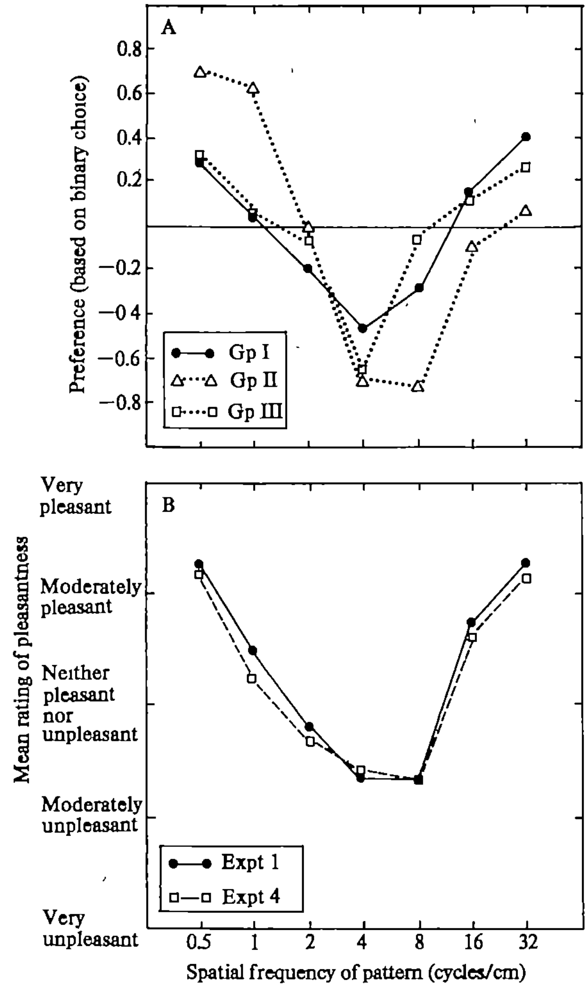


FIG. 2. Preference for square-wave gratings as a function of spatial frequency (Experiment 1). A, data from comparisons of pairwise combinations of gratings. Group I received the pairs in random orders, Group II received the low spatial frequencies first and Group III the high frequencies first. B, data from ratings (Experiments 1 and 4).

order of presentation. These range effects were not sufficient to affect the overall shape of the preference function. The individual ratings illustrated in fig. 2B also showed a significant effect of spatial frequency ($\chi^2 = 59.26$, d.f. $= 6$, $P < 0.001$, Meddis, 1980), with a significant quadratic component ($Z = 7.29$, $P < 0.001$, Meddis, 1980).

When invited to describe the effects that each pattern produced, the subjects listed both visual and nonvisual effects. In descending order of frequency the visual effects may be paraphrased as follows: colours (red, green, yellow, blue), diamond-shaped lattice, shimmer, blurring, dazzle, glare, bending of the lines, fading, 'blobs' and flickering. To our surprise, 11 of the 29 volunteers also listed adverse effects such as 'eyeache', tiredness, headache or 'dizziness'. The number of such complaints is shown as a function of spatial frequency in fig. 3. The number of complaints is high given that the pattern presentations were short and relatively few in number.

Relationship between Visual Illusions and Incidence of Headache

The next experiment was conducted in an attempt to determine whether headache might be the late result of prolonged observation of potentially epileptogenic patterns.

Experiment 2

The subjects were undergraduate physiology students at the University of Cambridge (28 men and 38 women aged 19 to 38 years) who were paid £1 for participating. For ethical reasons they were informed that there was a possibility that they might suffer a headache and persons with epilepsy or migraine were excluded. Two groups of volunteers were required to fixate the centre of a pattern of horizontal stripes for a succession of eight 10 s presentations. After each they noted the illusions they saw using the following checklist: 'blurring', 'shimmering', 'flickering', 'bending of the lines', 'shadowy shapes', 'red', 'yellow', 'green', 'blue'. The gratings were similar to those used in Experiment 1 but had a

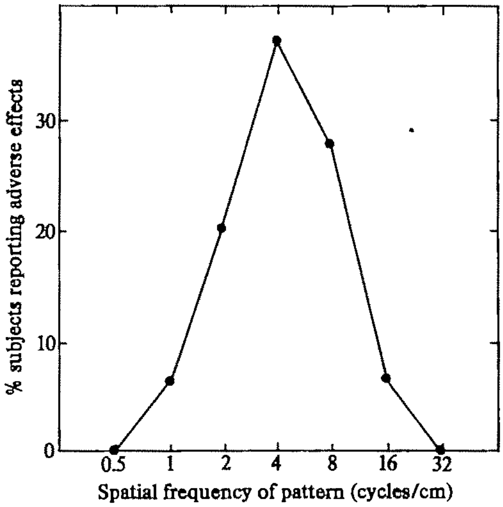


FIG. 3. Complaints of adverse nonvisual effects following the observation of gratings, expressed as a function of spatial frequency (Experiment 1).

TABLE 1. MEAN NO OF ILLUSIONS REPORTED IN EXPERIMENT 2

4 cycle/cm group	*No. of subjects*	*Mean no. of illusions*	*SD*	*t*	*P*
First day					
Headache	12	35.0	11.3	3.18	< 0.005
No headache	23	24.6	7.3		
Third day					
Headache	6	25.5	9.0	< 1	
No headache	29	28.7	10.3		
0.5 cycle/cm group					
First day					
Headache	11	14.3	7.2	< 1	
No headache	16	14.6	8.0		
Third day					
Headache	5	16.6	8.0	< 1	
No headache	22	14.0	7.5		

spatial frequency of 4, or 0.5 cycles/cm, depending on the subject group. The mean luminance was about 20 cd/m^2. The volunteers were asked to keep a diary of their headaches for the subsequent seven days. A week later they were told that in order to control for the effects of suggestibility they had been randomly allocated to 'experimental' or 'control' groups, and they were asked to guess in which group they had been placed. They were then asked to guess the purpose of the study.

Results. There was no significant difference between the groups with respect to the proportion of students (about 50 per cent) who correctly perceived the general purpose of the study, or with respect to the proportion (also about 50 per cent) who thought they had been allocated to the experimental condition. However, the large number of students who correctly perceived the general purpose of the study makes interpretation of the results difficult. Table 1 summarizes the main findings. Subjects in both groups reported fewer headaches on the third day than on the first, probably because of decreasing interest in the study but possibly because of an induction of headaches on the first day as a result of pattern viewing. Subjects in the 4 cycles/cm group who suffered a headache on the first day tended to have checked more illusions. As can be seen from Table 1, this relationship is statistically highly significant ($t = 3.18$, $P < 0.005$). The number of illusions seen was not significantly related to the age or sex of the subjects.

The above results were inconclusive as regards the induction of headaches by patterns but they suggested a possible relationship between headache susceptibility and the illusions seen in a pattern of horizontal stripes with a spatial frequency of 4 cycles/cm. Experiments 3 to 5 were designed to determine whether this finding was replicable.

Subjects were asked to estimate the incidence of their headaches over the last twelve months by responding to questions similar to the following. 'Think of headaches that you have had over the last month and whether they have been getting more frequent or less frequent. Use this information to help you estimate how many headaches you have had in the last twelve months.' Pilot studies had shown subjects' replies to this question to be reliable and relatively unbiassed. In the first pilot study sixth-form students (aged 17 to 19 years) were asked to estimate the annual incidence of their headaches, the number of headaches suffered in the previous seven days and the date of their last headache. The latter estimate was used to derive the time elapsed since the last headache. The Spearman rank correlations obtained between the three alternative measures of headache incidence were all greater than 0.5 and statistically significant. In the second pilot study a group of 55 women on the Applied Psychology Unit panel (aged 23 to 64 years) were asked to keep a headache diary for a month. The correlation between the incidence of headaches recorded in the diaries and the subjects' previous estimate of the annual incidence of their headaches is shown in fig. 4. It can be seen there is no consistent bias towards overestimation or underestimation of headache incidence. The scatter may be attributed to the short sampling period of one month, and to the inaccuracy of subjects' memory for their headaches. The rank correlation ($r_s = 0.66$) is nevertheless sufficiently high to lend credence to subjects' estimates.

Relationship between Susceptibility to Headaches and to Visual Illusions

Estimates of the annual incidence of headaches were used in the next three experiments in an attempt to determine whether there existed a relationship between headache susceptibility and illusions. For ethical reasons subjects with migraine and epilepsy were excluded.

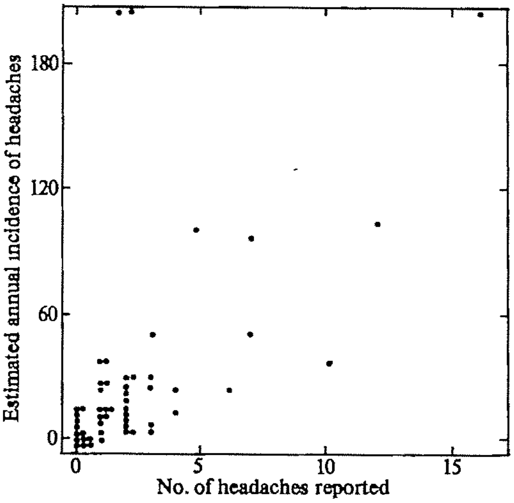


FIG. 4. Scatterplot showing the correlation between subjects' estimates of the annual incidence of their headaches and the number of headaches occurring in the subsequent month (pilot experiment).

Experiment 3

A group of female nursing and physiotherapy students aged 18 to 23 years from Addenbrookes Hospital, Cambridge was tested. The students were asked to estimate how many headaches they had had in the last twelve months. They then observed a printed pattern of horizontal stripes for 30 s at a distance of about 40 cm before checking the illusions they saw on the following list: 'fading of the pattern', 'bending of the lines', 'blurring', 'shimmering', 'flickering', 'colour', 'shadowy lines that are not really there', 'other (please specify)...'. Twenty-eight of the students, selected at random, observed a print of a horizontal square-wave grating with a spatial frequency of 4 cycles/cm. The remaining 26 students observed a grating with a spatial frequency of 0.5 cycles/cm. The gratings were similar to those used in Experiment 1. They were illuminated by overhead 100 Hz fluorescent lights and had a mean luminance of about 200 cd/m^2.

Results. The Spearman rank correlation between the estimate of the annual incidence of headaches and the number of illusions checked was 0.44 ($P < 0.05$) for the students who observed the 4 cycles/cm pattern and 0.03 for the students who observed the 0.5 cycles/cm pattern. The scatterplot for the 4 cycles/cm condition is shown in fig. 5.

These results confirm the spatial frequency selectivity of the relationship between illusions and headaches seen in Experiment 2. Experiment 4 was designed to test the extent of this selectivity.

Experiment 4

Eighteen men and 19 women aged 18 to 76 years from the Applied Psychology Unit's panel acted as subjects. They were instructed first to position a printed pattern of horizontal stripes at a distance of about 50 cm, and to look at a point at the centre of the grating for 5 s. They were then asked to look at a white sheet of paper for a further 5 s, and to check off the effects that they experienced. The checklist included not only the visual effects described in Experiment 1 but also 'illusory stripes', 'twinkling dots streaming up and down', 'eyeache', 'headache', 'nausea' and 'dizziness'. A total of 6 square-wave gratings similar to those used in Experiment 1 with spatial frequencies of 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 cycles/cm were presented in a random order. A further set was then presented in a different random order and the subjects were asked to rate the pleasantness of each pattern on a scale similar to that used in Experiment 1. The conditions of illumination were similar to those used in the previous experiments.

The subjects also completed a questionnaire that asked not only about the annual incidence of headaches but about their severity and locus. Questions about precipitating, exacerbating and alleviating factors, associated symptoms and variability were also included. In addition subjects were asked whether they had 'seen a doctor about their headaches'. At the end of the questionnaire subjects were asked to estimate how frequently they suffered the following symptoms: 'irritation or soreness of the eyes, dryness of the eyes, redness of the eyes, temporary blurring of vision (despite glasses if worn), spots or shapes in front of their eyes, faint colours surrounding objects, pain in response to light, narrowing of vision (one or both sides), any other visual problems' (Mackay, 1980).

Results. Table 2 presents the 2 × 2 contingency tables relating the illusions seen during observation of the pattern to subjects' estimates of the annual incidence of their headaches (illusions seen after observation of the pattern were not included). The relationship is largest for the grating with the spatial frequency of 4 cycles/cm ($r_s = 0.49$, $P < 0.05$) and this is not simply because more illusions were seen. Fig. 5 shows the scatterplot of the 4 cycles/cm condition. There were no significant effects of age or sex.

TABLE 2. CONTINGENCY TABLES SHOWING SEPARATELY FOR EACH SPATIAL FREQUENCY THE RELATIONSHIP BETWEEN SUBJECTS' HEADACHE SUSCEPTIBILITY AND THE NO. OF ILLUSIONS THEY REPORTED IN EXPERIMENT 4

Spatial frequency (cycles/cm)	*Headache susceptibility*	*Illusions reported*			
		0	*≥1*	χ^2	*P*
0.5	Low	14	4		
	High	14	5	0.08	0.77
1.0	Low	9	9		
	High	8	11	0.23	0.63
2.0	Low	4	14		
	High	2	17	0.93	0.33
4.0	Low	14	4		
	High	4	15	11.90	0.00
8.0	Low	5	13		
	High	1	18	3.44	0.06
16.0	Low	9	9		
	High	4	15	3.39	0.06

An analysis of the questionnaire revealed that subjects with frequent headaches tended to suffer relatively severe pain ($r_s = 0.68$, $P < 0.01$). They tended to complain of more frequent irritation or soreness of the eyes, temporary blurring of vision, pain in response to light ($P < 0.03$, sign tests). Only three had ever consulted a doctor about their headaches and only one had done so within the last twelve months.

The mean ratings of pleasantness were closely similar to those obtained previously and they appear in fig. 2B.

In the remaining replication only the 4 cycles/cm grating was used.

Experiment 5

A group of 33 male undergraduates in theoretical physics at the University of Cambridge, aged 19 to 23 years, were asked each of the following questions in turn: 'Do you see colour or colours?', 'Do the lines appear to bend?', 'Do the lines seems to blur?', 'Does the pattern flicker?', 'Do the lines wobble or shimmer?', 'Do parts of the pattern disappear and reappear?' After each question the students were asked to look at the fixation point in the centre of the horizontal grating for a total of 5 s and then to turn the pattern over and answer 'yes' or 'no' to the question. The subjects were then asked to estimate the annual incidence of their headaches. The 4 cycles/cm pattern and conditions of illumination were similar to those previously used.

Results. The Spearman rank correlation between the number of visual effects reported and the estimates of the annual incidence of headache was 0.49 ($P < 0.05$).

Discussion

Experiments 3–5 show a positive correlation between peoples' estimate of the annual incidence of their headaches and the number of illusions they report having

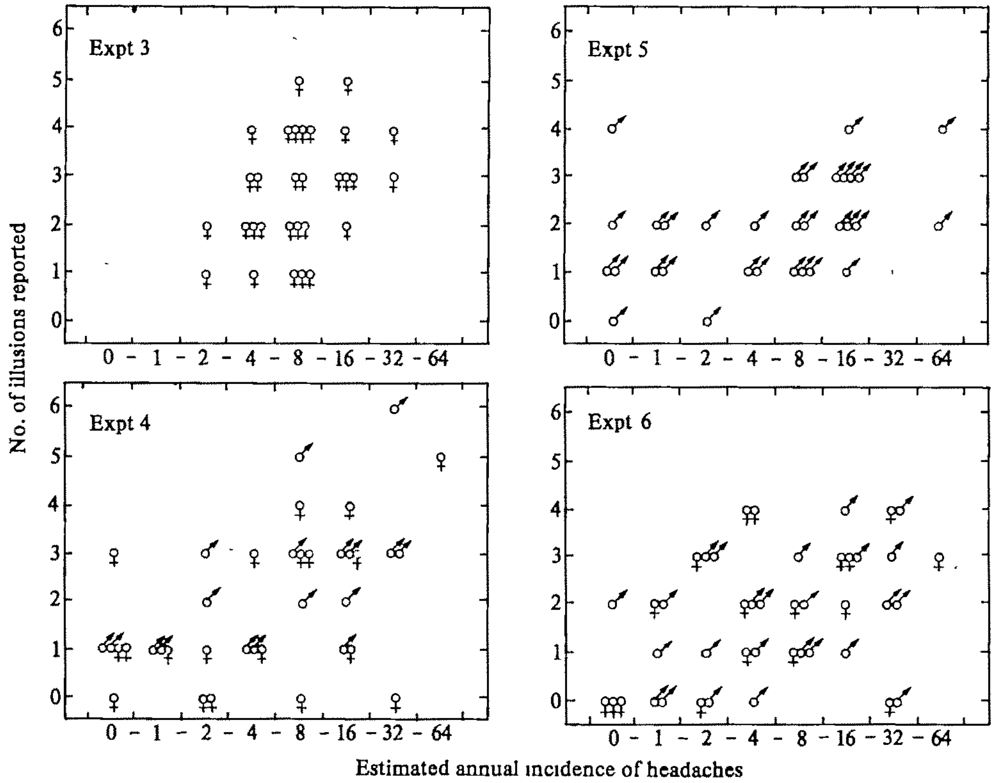


FIG. 5. Scatterplot showing the correlation between subjects' estimates of the annual incidence of their headaches and the number of illusions they saw in a grating with a spatial frequency of 4 cycles/cm (Experiments 3, 4 and 5).

seen in a pattern of stripes with a spatial frequency of 4 cycles/cm. Fig. 5 shows the relevant scatterplots for data obtained in Experiments 3, 4 and 5.

Two experiments (3 and 4) are consistent in demonstrating that the association between illusions and headaches obtains mainly for gratings with a spatial frequency of 4 cycles/cm and not for those with a lower frequency. The selective nature of the association would argue against the correlation being attributable entirely to subjects' suggestibility (some subjects being more prepared than others to admit to borderline headaches and borderline illusions). In two experiments subjects were asked not only about the incidence of their headaches but about other events (absentminded errors, in Experiment 4; episodes of back pain in another unpublished experiment). Any general contribution of suggestibility should produce a correlation between the reported incidence of these events and the number of illusions. In both cases the relevant rank correlation was negligible ($r_s = 0.07$; $r_s = 0.06$, respectively).

In the above experiments subjects were not asked whether they had a headache before they looked at the patterns. This was because in two pilot studies in which subjects were given an opportunity to report headaches at the time of testing only about 1 subject in 20 did so.

If the relationship between illusions and headaches was due to neurological factors rather than those of a more general nature it is possible that there might exist a relationship between the locus of head pain and the locus of illusions within the pattern. Such a relationship emerged in the experiments now to be described.

Relationship between Asymmetry of Illusions and Lateralization of Head Pain

Two studies were conducted: one with normal volunteers and the other with outpatients from a neurological clinic whose principal complaint was one of headache.

Experiment 6

Fifty panel volunteers (women aged 29 to 52 years) observed at a distance of about 40 cm a print of horizontal stripes (square-wave grating, spatial frequency 4 cycles/cm) in which the left and right halves were separated by a vertical black line 2 mm wide. They checked 'mainly on the left side', 'equally on both sides', or 'mainly on the right side' against the following list: 'colour', 'fading of the pattern', 'blurring', 'bending of the lines', 'shimmering', 'flickering', 'dots streaming up and down', 'shadowy lines that were not really there'. The volunteers later completed an extensive questionnaire concerning their headaches. This included questions about the usual localization of the pain: first, a checklist of items such as 'all over the head', 'left side only', 'right side only', etc., and second, four diagrams of the head (full face, back, left and right profiles) on which to shade the areas usually affected.

Results. Thirty-two of the 50 subjects reported both headaches and illusions, and in 6 the headaches were of an inconsistent lateralization. For the remaining 26 subjects the headaches were either bilateral or consistently on the same side. The

TABLE 3. ASSOCIATION BETWEEN REPORTS OF LATERALLY ASYMMETRIC ILLUSIONS AND REPORTS OF UNILATERAL HEADACHE IN EXPERIMENTS 6 AND 7

	Illusions in visual hemifields	
	Equal	*Unequal*
A. Panel volunteers		
Bilateral headaches	13	1
Unilateral headaches (consistent side)	6	6*
	$\chi^2 = 6.03, P < 0.05$	
B. Neurological patients		
Bilateral headaches	13	3
Unilateral headaches (consistent side)	8	14**
	$\chi^2 = 7.55, P < 0.01$	

* 5 maximal in ipsilateral field. ** 7 maximal in ipsilateral field.

significant association between the occurrence of asymmetric illusions and the occurrence of unilateral headaches is shown in Table 3A. Five out of the 6 subjects with both asymmetric illusions and consistent unilateral head pain reported illusions maximal on the *same* side as the head pain.

Experiment 7

In order to increase the sample of subjects with unilateral headache, neurological outpatients were tested. The patients all had a primary complaint of headache. Nine men and 37 women, aged 12 to 63 years from the Northern and Western General Hospitals, Edinburgh, were tested individually. They completed an extensive questionnaire about their headaches with items similar to those used in the previous study and in Experiment 4. Table 4 shows the number of patients with clinical diagnoses of headache as 'migraine', 'migraine and tension', 'tension' and 'depression'. The table also lists the number of patients in each of these categories complaining of clusters of symptoms found to be of importance in a factor analytic study of headache symptoms (Ziegler and Hassanein, 1982). Once they had completed the questionnaire the patients were shown a succession of 5 patterns of horizontal stripes, circular in outline and of increasing diameter, followed by 2 unilateral gratings, 1 in the left visual field and 1 in the right. The gratings had a spatial frequency of 4 cycles/cm and Michelson contrast of 0.7. The first five had radii of 7, 13, 25, 50 and 100 mm. Each bore a central fixation point. The unilateral gratings were formed by bisecting the largest pattern about a vertical midline. A fixation point was positioned 5 mm away from the middle of the straight edge of each half. All the patterns were mounted on grey card with a reflectance similar to that of the mean of the black and white stripes. The patterns were presented for 10 s each at a distance of 40 cm, after which the patients were asked to describe the illusions they saw using the following checklist: 'fading of the pattern', 'bending of the lines', 'blurring', 'shimmer', 'flickering', 'colours', 'shadowy lines', 'other'. When all the patterns had been presented they were asked to say whether one of the unilateral patterns had produced more illusions than the other.

Results. Table 3B shows the relationship between the inequality of the illusions seen in the two visual hemifields and the lateralization of headache as assessed by the questionnaire. Patients with a headache of inconsistent lateralization have been omitted. Note that once again persons who had bilateral headaches were unlikely to see asymmetric illusions. Seven of the 14 patients saw illusions mainly in the visual field ipsilateral to the pain. In other words, for this series, as for the last, there was little relationship between the side of illusions and the side of headache; the

TABLE 4. DIAGNOSES AND SYMPTOMS OF PATIENTS PARTICIPATING IN EXPERIMENT 7

	Diagnosis				
Headaches usually associated with	*'Migraine'* $(n = 24)$	*'Migraine and tension'* $(n = 5)$	*'Tension'* $(n = 7)$	*'Depression'* $(n = 2)$	*None* $(n = 8)$
Weakness or numbness	18	4	2	0	2
Loss of appetite, nausea, or vomiting	24	4	5	1	7
Visual precipitation or photophobia	18	5	5	1	3
Unilateral pain	21	4	2	1	4
Change in vision	20	3	2	1	1

relationship obtained simply in terms of presence of an asymmetry and the presence of unilateral headaches.

Patients with unilateral headaches are usually diagnosed as suffering from migraine rather than tension headache. From these considerations alone, a relationship between the presence of asymmetric illusions and a diagnosis of migraine might be anticipated. The association was significant and is shown in Table 5B. There was also a tendency for patients with a diagnosis of migraine to report seeing a greater number of different illusions (*see* Table 5A). The threshold radius at which illusions were first reported did not differ between the groups. Analysis of the individual illusions did not suggest that some were more discriminative than others.

TABLE 5 RELATIONSHIP BETWEEN ILLUSIONS AND DIAGNOSIS OF HEADACHE IN EXPERIMENT 7

		Headache diagnosis	
		'Migraine'	'Tension'
A. No. of different illusions	$\leqslant 2$	14	7
	> 2	10	1
		$\chi^2 = 2.26, P = 0.13$	
B. Symmetry of Illusions			
Symmetric		10	7
Asymmetric		14	1
	$\chi^2 = 5.06, P = 0.024$		

Responses to the individual questions on the questionnaire were reduced to binary scores by division about the median and submitted to a single link cluster analysis (Jardine and Sibson, 1971). The main clusters are summarized in Table 6. This shows that, with a few exceptions, the total number of illusions seen in all patterns is a variable that clusters together with symptoms of migraine. This clustering may reflect the relatively large proportion of patients with a diagnosis of migraine.

Latent class analysis was used in a subsequent statistical investigation of the data. Latent class analysis is a form of factor analysis applicable to discrete observations (Plackett, 1981, p. 105) and it hypothesizes the existence of (latent) groups of patients for which there are different rates of incidence of various symptoms. It estimates these rates and the probabilities of group membership and then infers for each patient, on the basis of his particular symptoms, the probability that he belongs to each group.

TABLE 6. SAMPLES OF ITEMS CLUSTERING MINIMALLY AND MAXIMALLY WITH TOTAL ILLUSIONS, SHOWING THE DIRECTION OF ASSOCIATION (EXPERIMENT 7)

Minimal	*Maximal*
Many alleviating factors (−)	Associated unsteadiness on feet (+)
Family history of high blood pressure (+)	Associated vomiting (+)
Pain in middle of forehead (+)	Last headache unilateral (+)
Associated ringing in ears (+)	Pain usually right-sided (+)
Meals generally appetizing (+)	Throbbing pain (+)
History of epilepsy (+)	Associated nausea (−)
Headaches start at same time of day (+)	Know it's coming (+)
History of ear complaints (−)	Associated loss of appetite (+)
Pain spreads (+)	Many exacerbating factors (+)
	Associated lightheadedness (+)
	Associated tender scalp (−)
	Associated change in vision (+)

Five symptoms were chosen arbitrarily: nausea, 'stuffed up' nose, tenderness of the scalp, changes in vision and prior warning. From these symptoms an assignment of the patient to two groups was derived. The groups were differentiated in the proportions 66 and 34 per cent and members of the larger group had a higher incidence of each of the five symptoms. This derived grouping had a significant association with (1) the clinician's diagnostic categories, when dichotomized as 'migraine' and 'other' and (2) with the occurrence of an above-median number of visual illusions.

In the subsequent replication using volunteers on the subject panel, few of whom had severe headaches, the cluster and latent groups analyses failed to reveal similar findings.

A second small-scale replication involved 27 patients from a neurological clinic and from general practice in Harlow, all of whom had a primary complaint of headache, diagnosed as migraine in all but 4 cases. In this study the questionnaire included, in addition to those items used in Experiment 7, items concerning the 9 ocular and visual symptoms listed in the description of Experiment 4. The number of patients who took part in the study was too small for the results of a cluster analysis to be reliable, but when the ocular and visual symptoms were subjected to an *a priori* analysis, 'temporary blurring of vision' was significantly associated with the total number of illusions reported (maximum $\chi^2 = 8.06$, d.f. $= 1$, $P < 0.02$).

Discussion

Experiments 3–7 are consistent in demonstrating a relationship between the headaches people suffer and the number and lateralization of the illusions they report when they look at certain striped patterns. The association between unilateral head pain and asymmetry of illusions is difficult to interpret in terms of peripheral ocular factors such as astigmatism, phoria or reduced acuity. The fact that the association was obtained despite an absence of any relationship between the direction of asymmetry and the side of pain is consistent with the weakness of the relationship between the side of visual aura and the side of head pain in patients with migraine headache (Peatfield *et al.*, 1981).

The statistical relationships reported above appeared only when relatively large groups of people were tested and it was not practicable for all the participants to receive an ophthalmological examination. However, in studies reported elsewhere, 17 volunteers who complained of 'eye-strain or headache' from reading were given an extensive ophthalmological investigation in addition to a test of illusion susceptibility. The ophthalmological findings were not associated with the illusions reported. The illusions, but not the ophthalmological findings, predicted the efficacy of a reading aid that covered the lines of text above and below those being read (Wilkins and Nimmo-Smith, 1984).

In the experiments reported above no attempt has been made to separate the illusions of colour, shape and motion. This is because there was no suggestion of a separate contribution to the relationship with headache. The relationship obtained only when the illusions were considered together. Such an approach is justifiable if it can be demonstrated that the illusions have a common neurological basis. As mentioned before, the evidence concerning the origins of the illusions is controversial, although central mechanisms have been postulated. The hypothesis of central mechanisms receives further support in the following experiments which demonstrate that various stimuli provoke illusions to the extent that they also evoke epileptiform EEG abnormalities in patients with photosensitive epilepsy. In these experiments, as in those above, analyses of the individual illusions was unproductive. It was the number but not the nature of the illusions that was related to the properties of the pattern.

SECTION 2

In studies of photosensitive patients (Wilkins *et al.*, 1980) it has been shown that the probability of epileptiform activity in response to a pattern depends on the following pattern parameters.

1. The shape of the pattern. If the component checks of a checker-board pattern are elongated in one direction the probability of paroxysmal activity increases with the logarithm of the length/width ratio (*see* fig. 6A).

2. The spatial frequency of the pattern. The spatial frequency optimal for the induction of paroxysmal activity depends somewhat on the angular subtense of the pattern, but for gratings subtending 20 deg is about 3 cycles/deg (*see* fig. 7A).

3. The duty cycle of the pattern. Duty cycle describes the relative width and separation of the component bars of a repetitive pattern in terms of the pulse/cycle fraction. The probability of paroxysmal activity is maximal when the width and spacing are in the ratio of approximately 1 : 1, that is, when the duty cycle has a value of about 50 per cent (*see* fig. 8A).

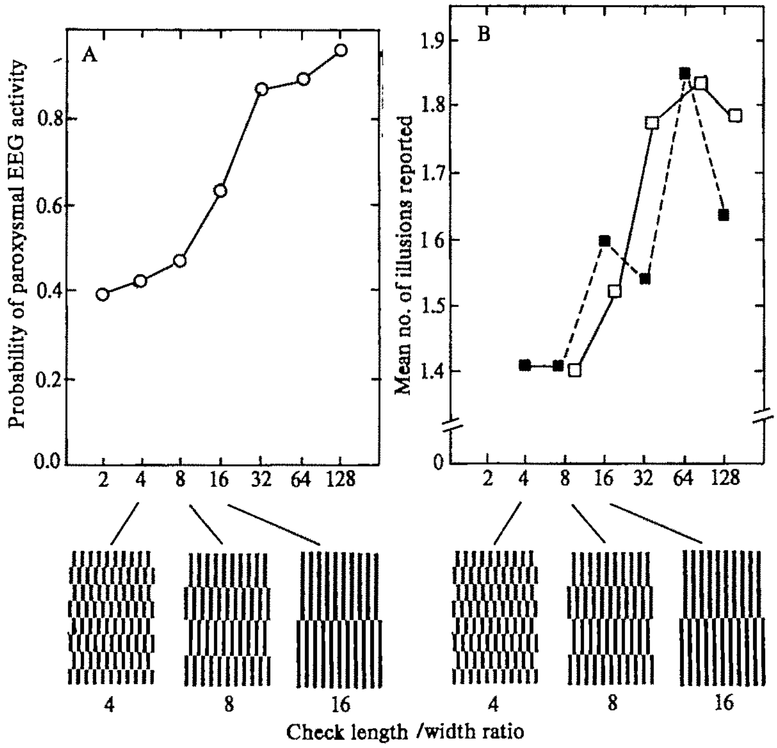


FIG. 6. A, probability of paroxysmal EEG activity as a function of check length/width ratio (*after* Wilkins *et al.*, 1979; one photosensitive patient, mean of 3 sessions). B, mean number of illusions reported by subjects without epilepsy, expressed as a function of check length/width ratio (Experiment 8) □——□ = 100 mm radius. ■- - - -■ = 80 mm radius.

4. The contrast of the pattern. The probability of paroxysmal activity increases with the Michelson contrast precipitously in the range 5–30 per cent, but thereafter shows little increase with further increases in contrast (*see* fig. 9A).

5. The size of the pattern. The size of the pattern can be varied in a number of ways (*see* introduction to Experiments 11 and 12). The probability of paroxysmal activity increases with size, and patients differ in the threshold size below which no paroxysmal activity appears.

6. The position of the pattern in the visual field. In general, patterns presented in the lateral hemifields (stimuli A and B, Table 9) are more epileptogenic than patterns of equivalent size presented in the upper and lower fields (stimuli C and D, Table 9). Some patients demonstrate marked differences in photoconvulsive threshold between the two lateral hemifields.

7. Monocular *versus* binocular presentation. The probability of paroxysmal activity is greatly reduced when presentation is monocular.

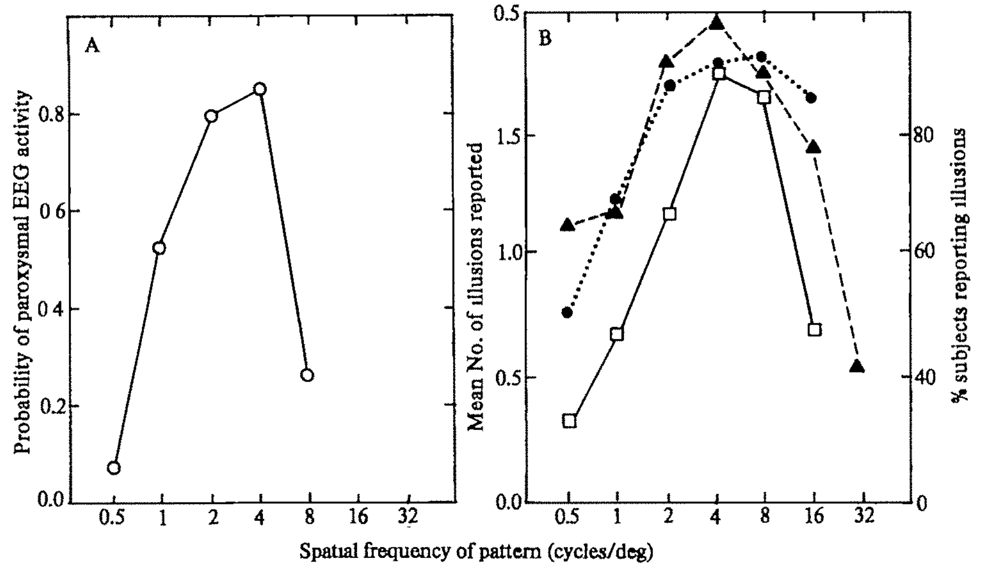


FIG. 7. A, probability of paroxysmal EEG activity as a function of the spatial frequency of a square-wave grating (*after* Wilkins *et al.*, 1979; mean of 8 photosensitive patients). B, mean number of illusions reported (□——□) by subjects without epilepsy (Experiment 4), and the percentage of subjects reporting illusions, expressed as functions of spatial frequency (Experiment 1 (▲----▲) and 4 (● · · ●)).

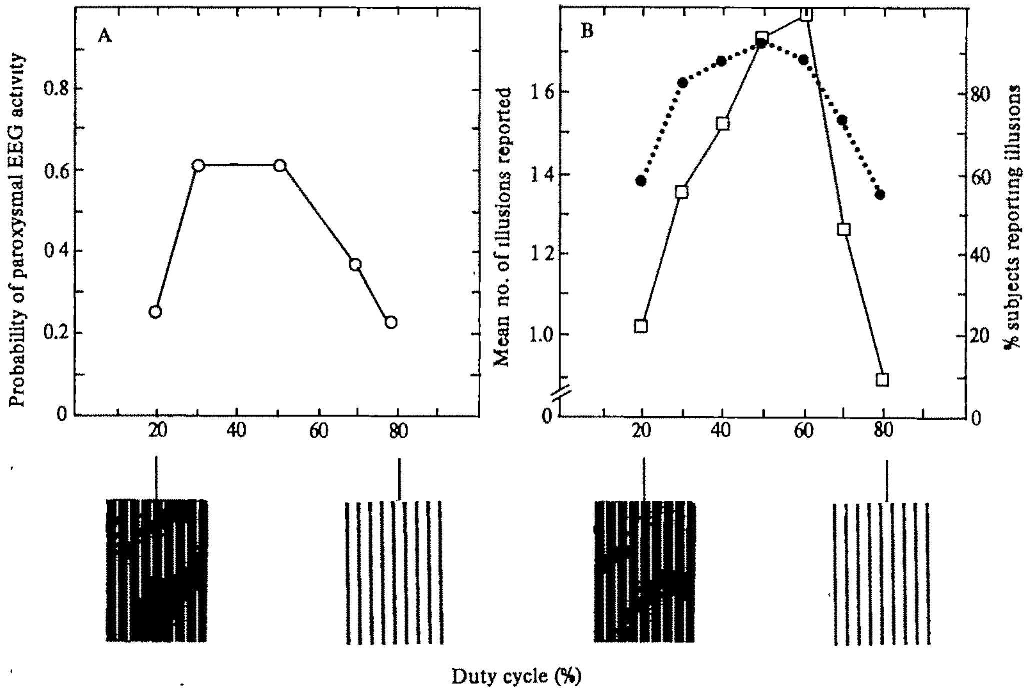


FIG. 8. A, probability of paroxysmal EEG activity as a function of the duty cycle of a square-wave grating (unpublished data, mean of 4 photosensitive patients). B, mean number of illusions reported (□——□) by subjects without epilepsy, and the percentage of subjects reporting illusions (● · · ●), expressed as a function of duty cycle (Experiment 9).

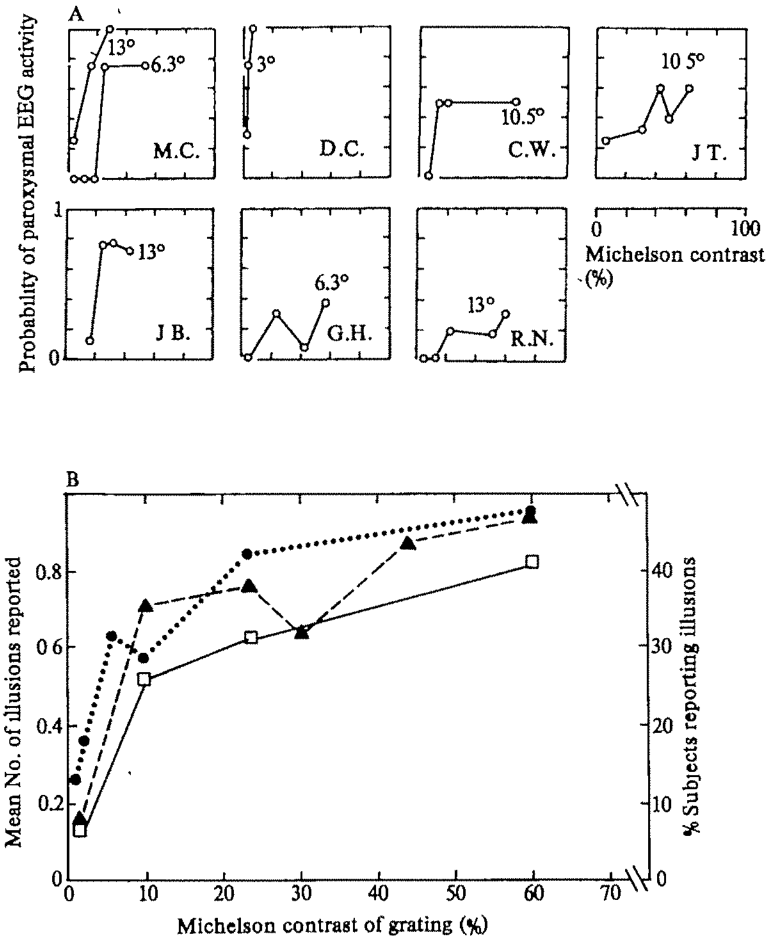


FIG. 9. A, probability of paroxysmal EEG activity as a function of the Michelson contrast of a square-wave grating (*after* Wilkins *et al.*, 1980). The data for each patient are shown in a separate panel, together with the radius of the grating in degrees of visual angle. B, mean number of illusions reported (□——□) by subjects without epilepsy, and the percentage of subjects reporting illusions (lin ▲- - - -▲; log ● · · ●), expressed as a function of contrast (Experiment 10).

Effects of the Spatial Frequency of a Pattern

The data from Experiment 4 (summarized in Table 2) have already shown how the number of illusions varies as a function of spatial frequency. These data have been plotted, together with those from Experiment 1, in fig. 7B. Despite the different procedures involved in Experiments 1 and 4, notably as regards in range of spatial frequencies under comparison and the absence of a formal checklist in Experiment 1, the percentage of subjects reporting illusions is a very similar function of spatial frequency. The mean number of illusions seen is calculated from the data of Experiment 4 and has a function very similar to that for the probability of paroxysmal activity (fig. 7A). In both functions the maximum is between 1 and 8 cycles/deg.

In the following experiments subjects without epilepsy were asked to report the illusions they saw in patterns that varied with respect to the remainder of the 7 parameters listed above.

General Procedure

The volunteers who took part in these experiments (members of the Applied Psychology Unit subject panel, 6 men and 105 women, aged 25 to 76 years) were tested in 6 groups. Each volunteer was presented with a booklet containing prints of patterns and was instructed to look at each print in turn for 10 s at a distance of about 40 cm, and then to check the illusions seen on the following list: 'red', 'green', 'blue', 'yellow', 'blurring', 'bending of stripes', 'shimmering', 'flickering', 'fading', 'shadowy shapes', 'other (please specify)'. The patterns were illuminated by overhead 20 kHz fluorescent tubes and the prints had a Michelson contrast of 0.7 and a mean luminance of about 100 cd/m^2.

Two groups (38 subjects in all) took part in Experiment 9. The 4 remaining groups each received a set of prints consisting of the patterns used in Experiments 8, 11, 12 and 13. The order of presentation was random and counterbalanced in the first group, random but constant in the second group, and random for the third and fourth groups. Since the data from the four groups were closely comparable they have been combined.

Data Analysis

The number of illusions reported was transformed before analysis in order to remove the effects of the large numbers of zero scores, according to the formula $\sqrt{(x+3/8)}$ suggested by Johnson and Leone (1964).

Experiment 8. Effects of Check Length

The patterns used are shown schematically in fig. 6. The component checks were 2.5 mm wide and the patterns were circular in outline with a radius of 100 mm (first and second groups) or 80 mm (third and fourth groups). The length/width ratio was determined by successive division of the pattern, beginning with a division through the centre. Thus the series 100 mm in radius had ratios of 160, 80, 40, 20 and 10, whereas the series 80 mm in radius had ratios of 128, 64, 32, 16, 8 and 4.

Results. The mean number of illusions is plotted as a function of length/width ratio in fig. 6B. It can be seen that there is a trend such that patterns with longer stripes elicit more illusions. The trend, as revealed by a linear regression analysis based on the transformed data, was significant for the data from the first and second groups ($t = 2.83$, d.f. $= 144$, $P < 0.01$) but not for the data from the third and fourth groups ($t = 1.57$, d.f. $= 165$, $P < 0.2$). The percentage of subjects reporting illusions varied from 82 to 91 per cent and showed no consistent trend as a function of check length/width.

When the illusions were analysed separately there was a tendency for fewer reports of 'red', 'green' and 'shadowy shapes' for the smaller length/width ratios, but this was not significant ($\chi^2 = 29.6$, d.f. $= 36$, $P = 0.76$).

Experiment 9. Effects of Duty Cycle

Seven gratings with a spatial frequency of 4 cycles/cm and a duty cycle of 21, 29, 42, 51, 62, 71 and 79 per cent were presented in different random orders. When they had checked the illusions seen, subjects were asked to reorder the gratings according to their personal preference for each.

Results. The mean number of illusions reported and the percentage of subjects reporting illusions are shown as a function of duty cycle in fig. 8B. For both functions the quadratic component was statistically highly significant ($t = 5.30$, d. f. $= 222$, $P < 0.001$; $Z = 4.01$, d.f. $= 6$, $P < 0.001$, Meddis, 1980).

When the individual illusions were analysed separately there was no indication that the proportion of illusions of the various types differed between patterns ($\chi^2 = 34.0$, d.f $= 54$, $P = 0.98$).

Subjects' mean rank of preference for the gratings was 4.5, 5.2, 5.2, 4.7, 3.9, 2.5 and 1.9 in order of increasing duty cycle, indicating a preference for gratings with extreme values. Both the linear and quadratic components of the trend were significant ($\chi^2 = 56.9$, d.f. $= 1$, $P < 0.001$ and $\chi^2 = 17.8$, d.f. $= 1$, $P < 0.001$, respectively).

Experiment 10. Effects of Pattern Contrast

Forty-one women on the Applied Psychology Unit panel (aged 18 to 68 years) were tested individually. They were asked to state their preference for 2 patterns that differed only in contrast. The patterns were black and white square-wave gratings, circular in outline and 20 deg in diameter, which had a spatial frequency of 3.3 cycles/deg and a mean luminance of 20 cd/m^2. They were viewed through apertures in a box containing an oblique semisilvered mirror that superimposed optically the images of two fields, one containing a print of the grating and the other a grey unpatterned surface with the same mean reflectance. Linear polarizers were positioned over each field and orientated so that the plane of polarization was horizontal for one field and vertical for the other. Two viewing apertures, one immediately above the other, were covered by polarizers and the subjects gaze was directed first through one aperture and then the other. The orientation of the polarizers controlled the relative attenuation of the two fields so that the apparent contrast of the pattern differed for the two apertures, although its mean luminance was identical. The subject was instructed to compare the pattern seen through the two apertures and to give a preference for one of the two contrasts. She was also asked to report any illusions she saw and to indentify the aperture through which they were seen. The checklist was identical to that given in the General Procedure. Eight levels of contrast were compared: 1, 2, 6, 11, 23, 33, 44 and 60 per cent. These were divided into two sets of six: 1, 11, 22, 33, 44 and 60, and 1, 3, 6, 11, 22 and 60. Four levels of contrast were common to each set, but in one set the spacing was approximately linear and in the other approximately logarithmic. The pairwise combinations of the stimuli in each set were compared in two consecutive series of 15 trials. Half the subjects received the logarithmic set first and the linear set second, and half received the sets in reverse order.

Results. For the group as a whole there was no consistent preference for one grating contrast over another. Nevertheless if subjects reported seeing illusions in one of a pair of gratings then they almost invariably preferred the other ($P < 0.001$, sign test). Fig. 9B shows the percentage of subjects reporting illusions, and the mean number of illusions reported, as a function of grating contrast. There was no significant effect of the order of presentation of the linear and logarithmic sets and so the data have been collapsed across this variable. It will be noted that the percentage of subjects reporting illusions is a similar curvilinear function of contrast, regardless of whether the data were obtained from the sets of stimuli that were linearly or logarithmically spaced. The mean number of illusions reported has been derived from both sets. When the illusions were analysed separately there was a tendency for relatively few reports of 'shimmering' at low contrasts, but the proportion of illusions of each type did not differ significantly as a function of contrast ($\chi^2 = 25.8$, d.f. $= 18$, $P = 0.1$).

From the shape of the functions shown in fig. 9B it is obvious that there is a sharp increase in the number of illusions seen when the pattern contrast is less than 30 per cent, although at contrasts above 30 per cent the illusions increase relatively little with contrast. In this respect at least the function is similar to that for the probability of paroxysmal activity in photosensitive patients shown in the panels in fig. 9A. The mean probability across patients is approximately linear when plotted as a function of log contrast, as is the function for the mean number of illusions.

Effects of Pattern Size

In photosensitive patients the probability of paroxysmal activity in response to patterns of stripes is critically dependent on the size of the pattern. Each patient has a different threshold size below which no paroxysmal activity occurs and above which the probability of paroxysmal activity increases with pattern size.

When gratings of concentric circles are cut as for the slices of a cake and opposed diametrically (Table 7) pattern size may be increased by increasing the angular size of the sectors. This has the advantage that all retinal eccentricities are affected by the change in size. If the probability of paroxysmal activity is plotted as a function of total pattern area the curves for different patients then appear to have roughly the

TABLE 7. MEAN NO OF ILLUSIONS REPORTED IN EXPERIMENT 11

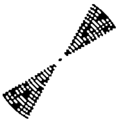
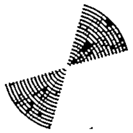
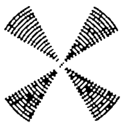
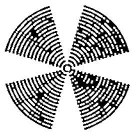
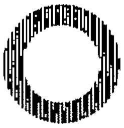
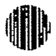
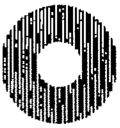
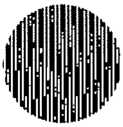
	Stimulus	*Mean no. of illusions reported*	*t*	*P*
A		0.56		
			1.09	< 0.15
B		0.68		
			0.18	n.s
C		0.68		
			2.39	< 0.01
D		1.03		

TABLE 8 PARAMETERS OF PATTERNS AND MEAN NO. OF ILLUSIONS REPORTED IN EXPERIMENT 12

	Stimulus	*Radii (mm)* *Inner*	*Radii (mm)* *Outer*	*Area* (*cm*^{2})	*Q** (%)	*Mean no. of illusions reported*	*t*	*P*
A		—	18	9	14	0.87		
							1.86	n.s.
B		65	100	181	14	1.00		
							2.49	<0 05
C		—	40	45	28	1.18		
							0.41	n.s.
D		39	100	269	28	1.20		
							2.69	<0.01
E		—	100	314	55	1.39		

* Percentage of visual cortex devoted to the analysis of the region of visual space occupied by the pattern, Drasdo (1977).

same slope but different x-intercepts. For most patients, the curves for patterns with four sectors (Table 7, stimuli C and D) overlap with the curves for patterns with two (Table 7, stimuli A and B): the two types of pattern are equally epileptogenic when they have the same total area (Wilkins *et al.*, 1980).

A different finding emerges when the gratings are straight lines, circular in outline, and pattern size is increased by increasing the pattern radius (Table 8, stimuli A, C, E). The functions relating the probability of paroxysmal activity to the area of the pattern have different x-intercepts, as before, but the slopes of the functions are no longer similar. The slopes resemble one another only when the probability is plotted as a function of the logarithm of the pattern area: for each patient the radius of the pattern has to be doubled to increase the probability from near zero to near unity (Wilkins *et al.*, 1979). This finding doubtless reflects the fact that the larger patterns now stimulate proportionately more of the peripheral retina, which has a smaller cortical representation. Such an interpretation is in line with the effects of selective stimulation of central and peripheral retina. When the central section of the pattern is removed so as to form a striped annulus (Table 8, stimuli B and D) the epileptogenic effects of the pattern are reduced by an amount that can be predicted from published estimates of the human cortical magnification factor. The total area of the pattern is not then predictive (Wilkins *et al.*, 1980).

In the experiments that follow, size was manipulated in each of the ways described above and normal subjects were asked to list the illusions they saw.

Experiment 11. Effects of Stimulation of Different Retinal Areas

The stimuli used are shown in Table 7. Half the two-sector patterns were rotated 90 deg to those shown. The concentric rings had a spatial frequency (diagonal measurement) of 4 cycles/cm, an outer radius of 100 mm, and the angles of the sectors were 30 or 60 deg.

Results. The mean number of illusions checked is shown in Table 7. Pairwise t-comparisons, based on the transformed scores, are summarized in the same table and indicate that the mean number of illusions for a pattern with two sectors was similar to that for a pattern with four sectors half the size. In patients with photosensitive epilepsy the probability of paroxysmal EEG activity is determined by the total pattern area, regardless of the number of sectors. The same is the case with respect to the mean number of illusions seen.

There was no significant differences between the four types of pattern with respect to the proportion of illusions of each type ($\chi^2 = 28.0$, d.f. $= 27$, $P = 0.4$) or the percentage of subjects reporting illusions ($\chi^2 = 4.3$, d.f. $= 3$, $P = 0.2$).

Experiment 12. Effects of Cortical Respresentation

The three complete gratings (stimuli A, C and E, Table 8) had radii of 18, 40 and 100 mm. The annuli (stimuli B and D, Table 8) had an external radius of 100 mm and internal radii of 65 and 39 mm, respectively The percentage of visual cortex devoted to analysing the region of visual space occupied by the pattern (Q) was estimated from Drasdo's (1977) equation:

$$Q = 100\,[1 - \exp\,(-0.0574\theta)]$$

where θ is the angular radius of a circular region, centrally fixated. Assuming a viewing distance of 400 mm, the value of Q for the annulus with the large internal radius (stimulus B) was identical to that of the smallest complete grating (stimulus A). The values of Q for stimuli C and D were identical and twice those for stimuli A and B. The largest complete grating (stimulus E) had a Q-value twice that for stimuli C and D and four times that of stimuli A and B.

It is unlikely that the patterns stimulate a constant proportion of the cortical cells responsible for analysing the region of visual space that each pattern occupies. The annuli had the same spatial frequency as the complete gratings (4 cycles/cm), and no account was taken of the changes in acuity with eccentricity, so the proportion of available cells actually stimulated was likely to differ considerably. Nevertheless, using similar stimuli, Wilkins *et al.* (1970) have shown that the probability of paroxysmal activity is better predicted by the value of Q than by the area of the pattern. The annuli had an area more than five times that of the discs with the equivalent Q-value, as can be seen from Table 8.

Results. The mean number of illusions reported is shown separately for each pattern in Table 8. Planned t-comparisons between pairs of stimuli yielded significant t-values for pairs with different estimates of Q (stimuli B and C, and stimuli D and E) but not for pairs with similar Q-values (stimuli A and B and stimuli C and D). The mean number of illusions increased with Q but not with pattern area, as can be seen from Table 8.

When the individual illusions were analysed separately, there was a tendency for annuli to evoke more frequent reports of shimmer and blurring, but this was not

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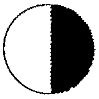
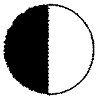
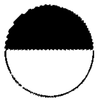
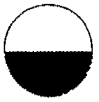
significant ($\chi^2 = 34.5$, d.f. $= 36$, $P = 0.56$). The percentage of subjects reporting illusions did not differ significantly for the pairwise comparisons shown in Table 8.

Experiment 13. Effects of Hemifield Presentation

Subjects in the first group were asked to check the illusions they saw in gratings similar to those represented schematically in Table 9; these were square-wave gratings, spatial frequency 4 cycles/cm, hemiradius 100 mm, with bars orientated at 45 deg to the vertical, half with an orientation 90 deg to that illustrated. The central fixation point was positioned 4 mm from the straight edge.

Results. The mean number of illusions reported is shown in Table 9. There were no significant differences between the patterns, F(3, 57) = 1.12, $P = 0.34$.

TABLE 9 MEAN NO. OF ILLUSIONS REPORTED IN EXPERIMENT 13

	Stimulus	*Mean no. of illusions reported*
A		2.10
B		2.15
C		1.95
D		2.55

Experiment 14. Effects of Monocular Viewing

The subjects who took part in Experiment 10 were earlier required to look at a succession of five patterns of increasing size, similar to those used in Experiment 7, for 5 s each. The largest pattern was then viewed monocularly with first the left and then the right eye, the other eye being covered. The pattern was then viewed binocularly once again.

Results. The mean number of illusions reported and the percentage of subjects reporting illusions are shown in Table 10. Both measures show an increase with pattern size (the linear trend is significant for mean number: t = 2.13, $P < 0.05$ and for the proportion of subjects reporting illusions: Z = 2.25, $P = 0.011$, Meddis, 1980). The mean number of illusions reported is significantly smaller under monocular viewing conditions than under the equivalent binocular conditions (t = 2.72, $P < 0.01$) but the proportion of subjects reporting illusions does not show a difference (Z = 1.24, Meddis, 1980). When the illusions were analysed separately, the proportion of illusions of each type was similar under monocular and binocular viewing conditions ($\chi^2 = 19.16$, d.f. $= 27$, $P = 0.86$).

TABLE 10. MEAN NO OF ILLUSIONS REPORTED AND PERCENTAGE OF SUBJECTS REPORTING ILLUSIONS IN EXPERIMENT 14

Pattern radius (mm)	*Viewing condition*	*Mean no. of illusions reported*	*% subjects reporting illusions*
7	Binocular	0.17	17
13	Binocular	0.78	61
25	Binocular	1.17	80
50	Binocular	1.46	90
100	Binocular	1.73	90
100	Left eye	1.34	80
100	Right eye	1.32	78
100	Binocular	1.54	83

Discussion

Experiments 8-14 have demonstrated that, with one exception, the parameters of patterns optimal for the induction of visual illusions are precisely those optimal for evoking paroxysmal EEG activity in patients with photosensitive epilepsy. This would suggest that the neural mechanisims responsible for the illusions may resemble, to some extent, those that trigger epileptic disturbances. The final experiment lends support to this view. Loss of sleep is one of the factors classically associated with a reduction of convulsive threshold. Experiment 15 demonstrates that the number of illusions reported increases after sleep deprivation.

Experiment 15. Effects of Sleep Loss

Eight female high school students aged 17 or 18 years (without epilepsy or migraine) were recruited for a study of the effects of deprivation of sleep on the EEG architecture of subsequent recovery sleep. For two initial nights the subjects slept in the EEG laboratory from about 11 p.m. to about 8 a.m. On the third night their sleep was interrupted at 4.00 a.m. and they remained awake until about 8 p.m. the same day when they were allowed to sleep for a variable period of time. The subjects then slept at home for the subsequent three nights, before returning to the laboratory for a further four nights on a regime identical to that undergone the previous week. Before and at least one half-hour after each period of laboratory sleep, and at 8 a.m. on the morning of the early awakening, subjects observed a succession of horizontal gratings similar to those used in Experiment 7 but 13, 25, 50 and 100 mm in radius. After observation of each pattern they completed a checklist identical to that described in the General Procedure. Subjects were informed only that this test was being given on behalf of a colleague.

Results. The total number of illusions per test for each of the 8 subjects is shown as a function of time in fig. 10. The perturbation at 4 a.m. is obvious. The mean number of illusions reported at 8 a.m. on the two mornings following interrupted sleep is greater than the mean at 8 a.m. on the previous mornings in 7 of the 8 subjects ($P < 0.05$, sign test).

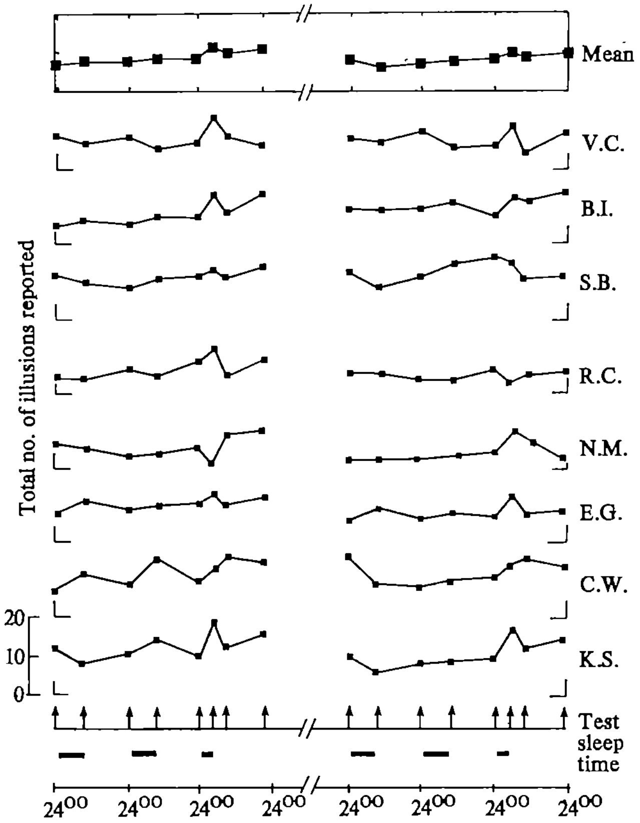


FIG. 10 Total number of illusions reported by individual subjects in Experiment 15 before and at least 30 min following sleep of about 8 h or 4 h duration.

GENERAL DISCUSSION

Certain patterns of stripes are unpleasant to look at, inducing anomalous visual effects and, less frequently, 'tired eyes' and headaches. The visual effects (illusions of colour, shape and motion) do not dissociate from one another, but all are induced by the same types of patterns. Their strength varies considerably from pattern to pattern and from person to person, but may nevertheless be measured using verbal descriptions of the various illusions produced. When normal subjects are asked to check the illusions seen on a list of such descriptions, the number but not the nature of the illusions checked is critically dependent on a range of pattern parameters. These include the shape, spatial frequency, duty cycle, contrast and angular subtense of the pattern, as well as its location in the visual field and whether it is viewed with one or both eyes. In patients with photosensitive epilepsy the probability of paroxysmal activity is dependent on the same parameters in almost precisely the same way. This would suggest that the neural processes that underlie the illusions may share mechanisms in common with those responsible for triggering epileptic disturbances. The increase in illusions following sleep deprivation supports such an interpretation. Photosensitive epileptiform abnormalities have been attributed to a minimal diffuse failure of cortical inhibition that may be GABAergic (Meldrum and Wilkins, 1984). Sensory stimulation that induces intense cortical excitation (possibly certain patterns of stripes) may cause a breakdown of inhibitory mechanisms that either remains localized or spreads. If the discharge remains localized within the visual cortex, neurons may nevertheless be inappropriately excited so as to produce anomalous visual effects, without any electrical disturbances being measurable at the scalp. If the discharge spreads further, EEG phenomena may be produced, followed ultimately by clinical seizures.

Stimulation of the two upper or two lower visual quadrants (upper and lower hemifields, stimuli C and D, Table 9) is generally less epileptogenic than stimulation by the same pattern of one of the lateral hemifields (stimuli A and B, Table 9; *see* Wilkins *et al.*, 1981). These differences have been attributed to the independence of the cerebral hemispheres in the induction of the epileptic discharge. Patterns that occupy the upper or lower hemifields stimulate both hemispheres, but stimulate each to a lesser extent than that to which one hemisphere is stimulated by a lateral pattern. The induction of a discharge is thought to require a 'critical mass' of excitation and this mass is more likely to be achieved within one hemisphere by a lateral pattern. The absence of any differences between the illusions produced by stimulation of the lateral and the upper and the lower fields is consistent with the view that the neural processes involved are more localized than those that sustain epileptogenic disturbances.

If the illusions are indeed the result of a failure of cortical inhibition their variation from individual to individual acquires a new significance. Persons who report many illusions tend to suffer frequent headaches and if the headaches are unilateral the illusions tend to be asymmetric. These findings would tend to support the existence of a relationship between headaches and cortical inhibitory mechanisms, as already proposed on the basis of EEG responses to intermittent light by Goldensohn (1976). The upper frequency limit of the photoconvulsive response to diffuse intermittent light is generally higher in photosensitive patients who are pattern sensitive than in those who are not. There is no difference with respect to the lower frequency limit (Wilkins *et al.*, 1980). This selective association between the effects of patterns and high frequency intermittent light is of interest because in patients with migraine the amplitude of the steady state evoked potential is abnormally high for flash frequencies above 20 Hz (Golla and Winter, 1959; Jonkman and Lelieveld, 1981).

If a relationship between cortical inhibition and headaches does exist, it need not necessarily be causal, although two observations suggest that it might be: (1) a substantial proportion of patients with migraine report visual precipitants broadly similiar to those that trigger seizures (Debne, 1984) and (2) about 40 per cent of patients with photosensitive epilepsy report 'various forms of ocular discomfort (headache, sore eyes, etc.) induced by potentially epileptogenic stimuli' (Kasteleijn-nolst Trenite *et al.*, 1982). The mechanisms whereby pattern stimulation might give rise to feelings of discomfort or pain are too various and uncertain to justify extensive speculation.

ACKNOWLEDGEMENTS

We thank the volunteers who took part in the studies and who may have suffered a headache as a result. We also thank H. Baddeley, J. Beck, R. Bowden, A. N. Exton-Smith, B. Moore, C. Nex, S. Saimbi, L. Taylor and A. R. Vatcher for assistance with testing or with its organization, C. Frankl and D. C. V. Simmonds for artwork, and A. D. Baddeley, F. W. Campbell, M. A. Georgeson, P. G. Lawrence, E. C. Poulton, J. G. Robson and N. J. Wade for their comments on the manuscript. The measurements of epileptic photosensitivity were the result of collaboration between the first author and his colleagues C. D. Binnie and C. E. Darby, without whose inspiration and support this paper would not have been written.

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(*Received August 12, 1983. Revised May 8, 1984*)

Brain (1984), **107**, 1019–1032

ISOLATED ABDUCENS NUCLEUS DAMAGE DUE TO HISTIOCYTOSIS X

ELECTRO-OCULOGRAPHIC ANALYSIS AND PHYSIOLOGICAL DEDUCTIONS

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SUMMARY

A case of complete rightward conjugate gaze paralysis, with electro-oculographic recordings, is reported. The only additional feature on clinical examination was a right infranuclear facial paresis. Radiographs of the chest showed multiple infiltrates in both lung fields; lung biopsy with ultrastructural study led to the diagnosis of histiocytosis X. A CT scan showed a single small tumour-like lesion, hyperdense and clearly defined, lying centrally in the fourth ventricle with a small ventral extension located just to the right of the midline. With appropriate treatment all the clinical signs rapidly subsided, together with the disappearance of the right ventral extension of the lesion visible on the CT scan.

The clinical and CT scan data suggested that the initial parenchymatous damage almost exclusively involved the right abducens nucleus, a structure which is very rarely affected in an isolated manner. Both main clinical features of the abducens nucleus syndrome which distinguish it from the recently described paramedian pontine reticular formation syndrome were present, namely absence of all ipsilateral conjugate movements and persistence of ipsilaterally directed saccades in the contralateral hemifield of movement. Furthermore, differences between peak velocities of both eyes in oculocephalic movements suggested that a pathway analogous, at least functionally, to the ascending tract of Deiters described in the cat and in the monkey may exist in man. Lastly, some recent clinical data concerning this unusual cause of CNS damage are briefly reviewed.

INTRODUCTION

Lesions limited to the region of the abducens nucleus are rare, and focal parenchymatous involvement of the CNS by histiocytosis X is unusual. These two clinical rarities are combined in the following case. Its interest is principally physiological since the oculomotor syndrome probably resulted from selective and complete damage to the abducens nucleus, the final common pathway involved in all ipsilateral conjugate eye movements. Precise analysis with electro-oculographic recordings showed that this syndrome included in particular certain characteristics

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in oculocephalic movements which appear to confirm in man that the motoneurons of the medial rectus muscle receive a vestibular excitation by two anatomically and functionally different pathways.

CASE REPORT

A 20-year-old man, with no noteworthy previous medical history, had suffered from morning headaches since the beginning of November 1982. Over the same period he had noticed increasing difficulty in looking to the right without experiencing diplopia. On examination (November 10, 1982), there was a right infranuclear facial paresis and a complete conjugate gaze paralysis to the right. This was studied electro-oculographically on December 7, 1982 (*see* below). No other clinical abnormalities were noted.

A CT scan (November 10, 1982) showed a solitary small hyperdense tumour-like lesion, which enhanced after contrast injection. This was clearly defined, lying mainly in the fourth ventricle (fig. 1A). It lay in the midline and was elliptical in shape, with an oblique major axis. Its ventral tip was clearly located to the right and its dorsal tip to the left of the midline. There was no hydrocephalus. Radiographs of the chest showed multiple nodular infiltrates scattered in both lung fields, of variable size, with indistinct margins and some cystic changes. The diagnosis of histiocytosis X was established by lung biopsy, including an ultrastructural study which disclosed numerous typical X bodies in the cytoplasm of histiocytes. An extensive search revealed no other systemic involvement by the disease.

Treatment combining prednisone (1 mg/kg/day) with vinblastine (10 mg/week) was undertaken from December 7, 1982, at which time the neurological signs were identical to those observed initially. All the clinical neurological disorders subsided within two weeks, without occurrence of diplopia. A CT scan on December 22, 1982, just after this recovery, showed that the hyperdense lesion had diminished by half (fig. 1B). Now rounded (on all sections), the lesion had lost in particular its small ventral extension which had been clearly located to the right of the midline. Eleven months later a further CT scan showed that this lesion still had exactly the same appearances. The chest x-ray became normal after six months of treatment. Clinical examination was still normal at the beginning of December 1983, whereas the prednisone dose had been reduced by half since July.

OBSERVATIONS

Oculomotor Examination (*December 7, 1982*)

Eye movements were recorded separately for each eye using direct current electro-oculography. There was no strabismus and both eyes were in the midline at rest.

Horizontal saccades were performed to command and in response to the appearance of lateral visual targets (at 25 deg). Results were analogous with both types of stimulation. Leftward saccades were normal (fig. 2Aa). The return movement from the left position to the midline included one or two saccades, very slightly slowed. There was no movement when a rightward saccade was attempted from the midline (fig. 2Ab).

Horizontal foveal pursuit (tested with a small target moving slowly and smoothly) was only possible in the left hemifield of movement, being partly saccadic to the left

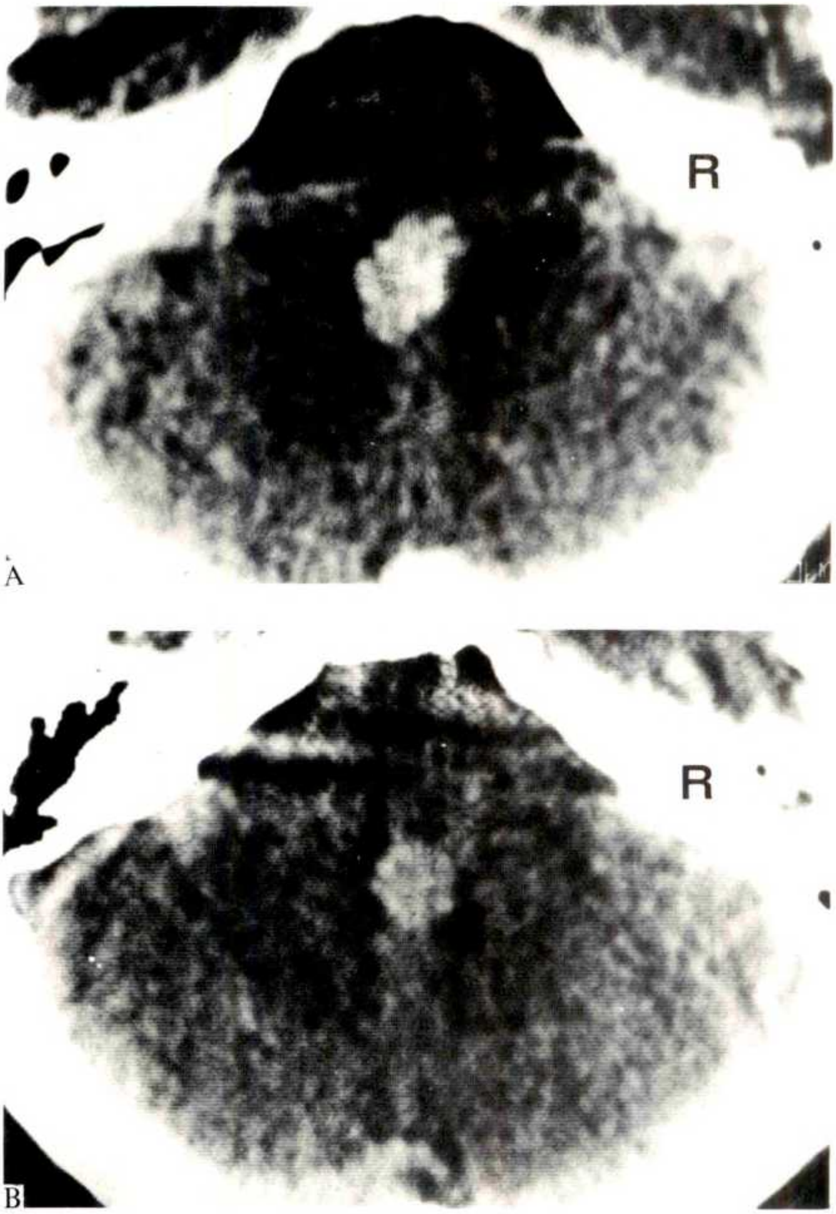

FIG. 1. CT scans (after contrast injection) at lower pontine level. A, first CT scan (November 10, 1982). An elliptical hyperdense lesion, with a ventral tip located just to the right of the midline lies in the fourth ventricle. B, second CT scan (December 22, 1982). The lesion has diminished, become rounded and has lost the small right paramedian ventral tip previously observed.

(fig. 2B), but also including at times one or two small saccades (directed to the right) in certain rapid return movements to the midline.

Horizontal oculocephalic movements were elicited by rapid passive rotations of the head in the light with visual fixation, and then in darkness without fixation. Results were identical in both cases. These reflex movements were performed only in the left hemifield of movement, both eyes moving normally to the left and returning to the midline, which could not be crossed to the right (fig. 2C). However, in the return from the left to the midline, it was noted that the velocity of each eye was clearly different, in spite of an equal amplitude of movement for both eyes. Peak velocity of the right eye was always less (at times twice as slow) than that of the left eye.

There was a small left-beating nystagmus in the left lateral position, appearing from 20 deg leftwards, with an amplitude slightly greater for the left eye (fig. 2D).

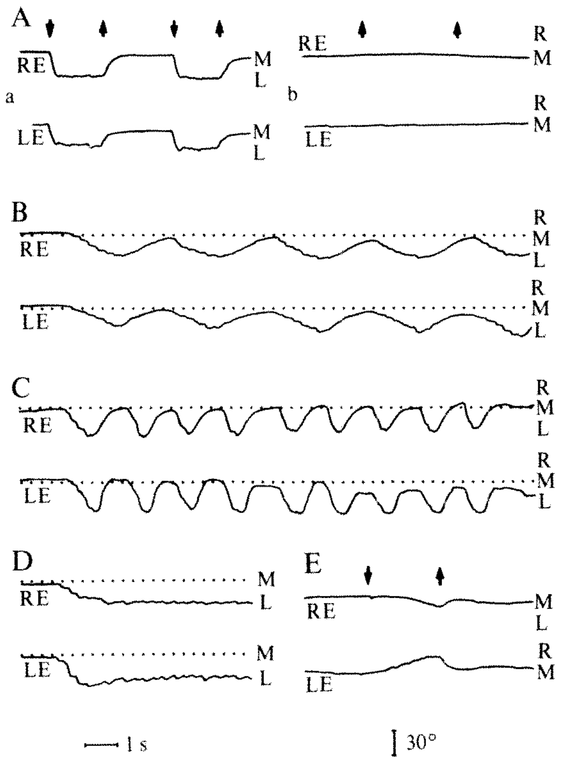

Fig. 2. Horizontal eye movements. An upward deflection indicates a rightward eye movement and on a downward deflection a leftward movement. L = left; LE = left eye; M = midline; R = right; RE = right eye. A, voluntary saccades: a, leftward saccades (downward arrows) are normal and return saccades (upward arrows) to the midline (directed rightwards) are only slightly slowed; b, rightward saccades (attempted at the upward arrows) are absent when the eyes are on the midline. B, foveal pursuit movement: these are only seen in the left hemifield of movement and are largely saccadic leftwards. C, oculocephalic movements: these are also only in the left hemifield of movement; note that peak velocity of the right eye is always less than that of the left eye in the return movement from left to the midline. D, left fixation: left-beating nystagmus. E, convergence (between both arrows): this is normal for the left eye but a little reduced for the right eye.

During leftward optokinetic stimulation (about 30 s, on a screen covering 70 deg of the visual field), as well as after caloric stimulation of the left ear with ice-cold water, no nystagmus was observed, nor any leftward eye movement, both eyes remaining on the midline. After reverse optokinetic and caloric stimulation a left-beating nystagmus was noted in both cases, with an amplitude a little greater than that of the gaze nystagmus previously described, but whose slow phases never crossed the midline to the right.

As soon as the lids closed the eyes moved slightly to the left and upwards. Convergence was normal for the left eye but a little reduced for the right eye (fig. 2E). Vertical eye movements—saccades, foveal pursuit, oculocephalic reflex and optokinetic nystagmus—were normal.

DISCUSSION

The interest of this case results from the particular location of the lesion, the pathophysiological consequences that ensued and the unusual cause.

Location of the Lesion

A complete rightward gaze paralysis, involving all lateral conjugate movements, was the essential clinical feature. Such a syndrome implies damage to the final common pathway of lateral eye movements, namely to the abducens nucleus. It has now been well established both in the cat (Graybiel and Hartwieg, 1974; Baker and Highstein, 1975; Graybiel, 1977; Highstein and Baker, 1978; Steiger and Büttner-Ennever, 1978) and in the monkey (Carpenter and Batton, 1980; McCrea *et al.*, 1982) that this nucleus contains both (1) motoneurons of the sixth nerve responsible for abduction of the ipsilateral eye and (2) internuclear neurons which decussate at the level of the abducens nucleus, pass through the medial longitudinal fasciculus (MLF) and terminate in the subdivisions of the oculomotor nucleus (Büttner-Ennever and Akert, 1981) mediating conjugate adduction of the contralateral eye. Furthermore, an oculomotor syndrome similar to that of this patient was induced in the monkey after selective destruction of the abducens nucleus (Carpenter *et al.*, 1963).

In man, acquired lesions strictly limited to the abducens nucleus are very rare. There is so far only one known clinicopathological case of a minute infarct of the abducens nucleus, in which the limits of this nucleus were not transgressed (Bennett and Savill, 1889). Lateral conjugate gaze paralysis was severe, with permanent deviation of both eyes towards the healthy side. Vestibular reflex eye movements were not tested. Only one other analogous case in which reflex eye movements were mentioned has, to our knowledge, been reported (Meienberg *et al.*, 1982). However, although at one time during the clinical course of this case there was a unilateral conjugate gaze paralysis for all types of lateral movements and an infranuclear facial paralysis, there was also an adduction paresis of the ipsilateral eye. Post-mortem study six months later revealed invasion of almost all the ipsilateral tegmentum by a lymphoma.

In our case, it is clear that the lesion visible on the first CT scan had a volume greatly in excess of that of the abducens nucleus. Nevertheless, given the isolated feature of the lateral conjugate gaze paralysis, it appears highly probable that the tumour lay mainly in the fourth ventricle and barely extended ventrally to the floor of the ventricle. Such a parenchymatous invasion was logically related to the ventral tip of the lesion visible on the CT scan, located to the right of the midline, and therefore it is suggested that this tip selectively involved the right abducens nucleus (lying near the midline and just ventral to the floor of the fourth ventricle). Indeed, since there was no internuclear ophthalmoplegia (INO), the right MLF, located just medial and slightly ventral to the abducens nucleus, was not impaired. The persistence of saccades directed to the right, in the return movements from the left position to the midline, suggested moreover that the right paramedian pontine reticular formation (PPRF), located ventral but also rostral to the abducens nucleus, was undamaged (Pierrot-Deseilligny *et al.*, 1979, 1982). The infranuclear facial paresis is easily explained by the fact that the fibres of the facial nerve pass around the abducens nucleus in its immediate vicinity. Lastly, the disappearance of all neurological signs, along with that of the right ventral tip of the lesion visible on the second CT scan, strongly supports the hypothesis of parenchymatous damage restricted almost exclusively to the right abducens nucleus.

Pathophysiological Considerations

The first point of pathophysiological interest of this case is that the oculomotor findings agree with both of the principal theories, recently proposed, which characterize the abducens nucleus syndrome and permit its distinction from selective damage to the adjoining caudal PPRF (Pierrot-Deseilligny *et al.*, 1981, 1982), namely (1) absence of all ipsilateral eye movements, including reflex movements and (2) persistence of ipsilaterally directed saccades in the contralateral hemifield of movement. Conversely, in the PPRF syndrome in man, as in the monkey, certain ipsilateral reflex movements are still present (Pierrot-Deseilligny *et al.*, 1978; Lang *et al.*, 1982; Pierrot-Deseilligny *et al.*, 1984; Henn *et al.*, 1984) and all ipsilateral saccades, including those which should occur in the contralateral hemifield of movement, are abolished (Cohen *et al.*, 1968; Goebel *et al.*, 1971; Pierrot-Deseilligny *et al.*, 1978, 1979; Henn and Büttner, 1982; Leigh and Zee, 1983). The physiological hypotheses accounting for the distinct clinical features of these two syndromes have already been discussed (Pierrot-Deseilligny *et al.*, 1981, 1982), and will only be briefly reviewed here.

In selective damage to one abducens nucleus, persistence of ipsilaterally directed saccades in the contralateral hemifield of movement is explained by the phasic inhibition which still occurs in the opposite abducens nucleus. Such inhibition leads to an abrupt pause of activity in the motoneurons of the antagonist muscles, namely in those of the contralateral lateral rectus, directly inhibited, as well as in those of the ipsilateral medial rectus which are suddenly defacilitated by the inhibition of the internuclear neurons of the MLF (Hikosaka *et al.*, 1980). Thus this pause of activity allows the eyes to return to the midline by saccadic movements, slightly slowed simply because of the absence of phasic excitation of the agonist muscles. The phasic inhibition is performed by the inhibitory burst neurons (IBN), whose cell bodies in the cat lie in the reticular formation caudal to the ipsilateral abducens nucleus (fig. 3), and whose axons terminate after decussation in the contralateral abducens

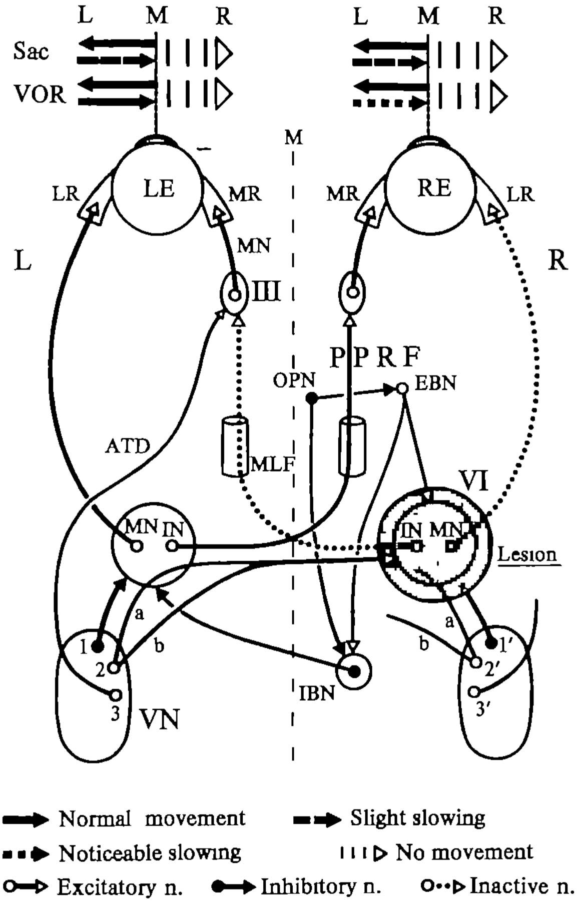

FIG 3. Diagram illustrating the organization of the motor and immediate premotor pathways involved in horizontal saccades and the vestibular ocular reflex. The nuclear tracts as well as the supranuclear pathways mainly involved in rightward movements are shown. The vestibular pathways mainly involved in leftward movements are outlined. ATD = ascending tract of Deiters; EBN = excitatory burst neuron; IBN = inhibitory burst neuron; IN = internuclear neuron; L = left; LE = left eye, LR = lateral rectus; M = midline; MLF = medial longitudinal fasciculus; MN = motoneuron; OPN = omnipause neuron; PPRF = paramedian pontine reticular formation; R = right; RE = right eye; Sac = saccades; VN = vestibular nucleus; VOR = vestibular ocular reflex. III = medial rectus subdivisions of the oculomotor nucleus; VI = abducens nucleus; 1-1′ = neurons terminating in the ipsilateral VI; 2-2′ = neurons terminating in the contralateral VI (a = passing through the ipsilateral VI and b = avoiding this nucleus); 3-3′ = neurons terminating in the medial rectus subdivisions of the ipsilateral oculomotor nucleus *via* the ATD.

nucleus (Hikosaka and Kawakami, 1977; Hikosaka *et al.*, 1980; Kaneko and Fuchs, 1981; Yoshida *et al.*, 1982). The activity of the IBN is controlled by the omnipause neurons (Nakao *et al.*, 1980) and probably also by the excitatory burst neurons (EBN) of the ipsilateral PPRF (Sasaki and Shimazu, 1981; Yoshida *et al.*, 1982), both located rostral to the abducens nucleus. As, in the tegmentum, the PPRF and the IBN are more ventral (and medial) than the abducens nucleus, the tracts linking both types of phasic neurons probably pass ventrally (and medially) at a distance from this nucleus. Thus all the circuitry involved in the phasic inhibition of the contralateral abducens nucleus avoids the area of the ipsilateral abducens nucleus, explaining why, after selective damage to this nucleus, return saccades from the opposite position to the midline persist.

On the other hand, in a unilateral lesion selectively involving the PPRF, the phasic excitation of the motoneurons of the agonist muscles, as well as the phasic inhibition of the motoneurons of the antagonist muscles, cannot be conveyed (fig. 3). Consequently, all ipsilaterally directed saccades are abolished, even those which should occur in the contralateral hemifield of movement; in particular, the voluntary return saccade from the contralateral position to the midline is replaced by an extremely slow movement whose velocity is about 10 to 20 deg/s, namely at least ten or twenty times slower than that of a saccade (Pierrot-Deseilligny *et al.*, 1982). Persistence of ipsilateral reflex movements in selective damage to the PPRF (involving its rostral as well as its caudal portion) may simply be explained by the existence of direct tracts between the vestibular and abducens nuclei, not implicating the PPRF (McCrea *et al.*, 1981).

Two further clinical features deserve comment in this case. The first is the absence of leftward slow phases after caloric and optokinetic (OKN) stimulation. It is not surprising that the existence of these two types of movement may at times be linked since it is generally admitted that the vestibular nuclei are an integral part of the pathways involved in OKN stimulation of the peripheral visual field (Leigh and Zee, 1983). This link would be especially apparent in circumstances where the foveal smooth pursuit system—which perhaps does not directly implicate the vestibular nuclei but largely participates in the OKN slow phase—is also affected, as it is here (saccadic leftward pursuit movement), for reasons which are not clear. Leftward slow phases are normally performed by the left abducens nucleus, here undamaged, and mainly controlled by the right vestibular nuclear complex (Baker *et al.*, 1981), located caudal and lateral to the right abducens nucleus which is impaired in this instance. It appears possible that in our case part of the excitatory vestibular tracts implicated in the slow phases of the abolished nystagmus were affected in their course between the right vestibular nucleus and the left abducens nucleus. Indeed, before decussation and their termination in the contralateral abducens nucleus, these tracts pass, in the cat, near and even through the ipsilateral abducens nucleus (Grant *et al.*, 1977; McCrea *et al.*, 1981), namely in the damaged area in the present case (fig. 3, neuron 2′a). How then can persistence of a leftward oculocephalic movement, which involves analogous premotor pathways, be understood in this patient? This could arise, both because (1) a part of the excitatory vestibular pathways terminating in one abducens nucleus probably avoids the area of the contralateral abducens nucleus (fig. 3, neuron 2′b), possibly passing through the nucleus prepositus hypoglossi or even through the ipsilateral vestibular nuclear complex and (2) the oculocephalic manoeuvre is much more effective than a simple caloric or OKN stimulation, as it directly implicates the two semicircular canals, along with the cervico-ocular reflex (Maeda, 1979), whose role could be noticeable in certain pathological states (Dichgans *et al.*, 1974; Peterson and Goldberg, 1982). However, without precise anatomical data in our case, and in the absence at this time of a full knowledge of the accurate course and actual functional role of the different efferent excitatory vestibular tracts, it would be speculative to go further.

The second feature results from the difference in peak velocity of both eyes in the return oculocephalic movement from the left position to the midline. The peak velocity of the right eye was almost twice as slow as that of the left eye, with no difference between the amplitudes of movements, since both eyes stopped on the midline. As the peak velocity of the left eye returning to the midline was approximately equal to that of both eyes moving leftwards, it appears first that there was a slowing of the right eye returning to the midline, and also, given the conjugate gaze paralysis affecting both eyes, that the left eye velocity in the same movement was surprisingly close to normal. To explain such a velocity difference it must be considered that an eye movement, even in a simple return to the midline, results from the concomitant activities of the antagonist and agonist muscles. In our case, during the return of both eyes from the left to the midline the defacilitation-inhibition exerted on the motoneurons of the antagonist muscles, namely the lateral rectus of the left eye and the medial rectus of the right eye, was most likely equal since both the left abducens nucleus and the right MLF, which are essentially involved in this mechanism (Pierrot-Deseilligny *et al.*, 1982), were undamaged. Consequently, a difference of excitation between the agonist muscles of both eyes may be suggested. No excitation in the motoneurons of the right lateral rectus could have occurred since the right abducens nucleus was damaged. On the other hand, it is possible that some excitation had reached the motoneurons of the medial rectus of the left eye, accounting for the higher velocity of this eye. Such an excitation could be mediated by a tract analogous to the ascending tract of Deiters, which has been described in the cat (Gacek, 1971; Baker and Highstein, 1978; Reisine *et al.*, 1981) and in the monkey (Lang *et al.*, 1979). This tract passes through the dorsal tegmentum, lateral to the MLF, and directly unites the ventral lateral vestibular nucleus with the motoneurons of the medial rectus of the ipsilateral eye, with no decussation (fig. 3). Its action is excitatory, the neuronal activity approximately encoding eye position in the orbit but being more especially modulated by head velocity during rotation in the horizontal plane (Reisine and Highstein, 1979; Highstein and Reisine, 1981), such as that performed in oculocephalic manoeuvres.

Two different pathways mediating excitatory vestibular messages to the motoneurons of the medial rectus, the first decussating twice, passing through the contralateral abducens nucleus and then into the ipsilateral MLF by the internuclear neurons, the second (the ascending tract of Deiters) not decussating, could therefore exist. However, it is clear that the pathway that decussates twice, although a little more complicated, plays the essential functional role in mediation of the vestibular excitation. Indeed, the burst-tonic activity of the internuclear neurons of the MLF is similar to that which is recorded in the motoneurons of the medial rectus during all lateral conjugate eye movements, including therefore vestibular reflex movements (King *et al.*, 1976; Pola and Robinson, 1978). Furthermore, when the internuclear neurons are damaged along their axons in an MLF lesion (Evinger *et al.*, 1977; Jenkyn *et al.*, 1978; Pierrot-Deseilligny and Chain, 1979; Kommerell, 1981) or at their origin either as here or in certain 'one-and-a-half' syndromes (Pierrot-Deseilligny *et al.*, 1981, Case 1), reflex stimulation does not allow the paralysed eye to adduct. The primacy of the pathway passing through the abducens nucleus and the internuclear neurons of the MLF does not exclude the possibility of a minor functional activity mediated another way, such as, for example, *via* the ascending tract of Deiters. This tract could be vestigial. Its function perhaps regressed when the motor centre of all lateral movements developed in the abducens nucleus in order to perfect the conjugate activity of both eyes in frontal-eyed species whose vision was becoming largely binocular. In such a hypothesis, the residual activity of the ascending tract of Deiters thus no longer allows the eye to cross the midline towards adduction when the internuclear neuron is damaged, but could still contribute to some extent to the elaboration of the velocity of the reflex movement directed inwards.

Cause

This case obviously has further clinical interest because of the relative rarity with which the nervous system is affected by histiocytosis X. It must first be accepted, however, that the neurological impairment also resulted from this disease since no histological proof for the nature of the pontine lesion can be provided. The coexistence of the pulmonary and neural involvement, as well as the partial regression of the latter with treatment, strongly support the case for a single cause. Neurological involvement in histiocytosis X may result from compression or invasion from a neighbouring bony focus (vertebral or cranial), from meningeal invasion, or from parenchymatous lesions (Kepes, 1979). Histologically, there is a benign proliferation of histiocytes, combined at times with eosinophilic granulocytes, leading to tumour-like masses (as probably in our case) or infiltration with varying degrees of demyelination (Rubens-Duval *et al.*, 1966). When the lesion is focal, the hypothalamic area is by far the most commonly involved, generally with diabetes insipidus. Outside this region, some cases with focal lesions, isolated or multiple, in the cerebellum (Beard *et al.*, 1970; Yamaguchi *et al.*, 1972; Adonarto *et al.*, 1980), the choroid plexus (Rosner, 1957; Morello *et al.*, 1967; Jaer *et al.*, 1973; Vaquero *et al.*, 1979), the parietal lobe (Khan *et al.*, 1980), the temporal lobe (Sivalingam *et al.*, 1977), and the spinal cord (Salcman *et al.*, 1974) have been reported. Another case with a pontine lesion, involving the middle cerebellar peduncle, is on record, combined, however, with damage to the hypothalamic area (Castaigne *et al.*, 1968). Focal cerebral lesions may be associated with involvement of other systems as in our case, and diagnosis is then relatively easy. At times the neural lesions are completely isolated and diagnosis is only possible after surgical operation, location permitting. A CT scan, however, may now facilitate diagnosis, especially when it shows, as here, a hyperdense enhancing tumour-like and relatively homogeneous lesion (Sivalingam *et al.*, 1977; Khan *et al.*, 1980).

ACKNOWLEDGEMENTS

The authors wish to acknowledge their gratitude to Dr M. Ferry who performed the CT scans, to Mr D. MacGregor for the English translation of the manuscript, and to Mrs S. Rivaud for her technical assistance.

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(*Received January 26, 1984. Revised April 3, 1984*)

Brain (1984), **107**, 1033-1072

IMPAIRMENTS OF VISUAL OBJECT TRANSFORMS IN MONKEYS

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SUMMARY

Monkeys were first trained on a series of standard, unchanging visual objects to obtain food reward. After reaching criterion on each subject, training with it continued but on 20 per cent of the trials the object was transformed in (1) size, (2) orientation, or in (3) its shadow configuration. Monkeys with lesions either of the inferotemporal cortex or the foveal prestriate region were impaired in identifying all three types of transforms as the rewarded object. They were also slightly impaired in continuing postcriterion high levels of performance on the nontransformed objects, but it was shown that the transform deficit was still present when this factor was partialled out. The groups with transform deficits were also impaired initially in their discrimination between solid cones of varying apical angle, although their final performance approached that of controls. The inferotemporal group, especially with the lesion placed anteriorly, had a deficit in their initial learning of the untransformed objects as well as in the retention of a preoperatively learned pattern discrimination; they were also deficient in selecting food objects from among an array of nonfood objects. No deficits were seen in animals with lesions of the parietal lobe or the fundus of the superior temporal sulcus in any task. The results and other relevant animal evidence are interpreted in terms of the view that the anterior temporal lobe is concerned with the storage of an object-centred prototype, necessary in turn for the attachment of positive or negative meaning, and the more posterior inferotemporal lesions with the addressing of view-centred visual information *en route* to the anterior regions. They are also consistent with the findings on the recognition of 'unusual views' made by Warrington and coworkers in patients with posterior lesions.

INTRODUCTION

In identifying a real object in everyday life, an observer must contend with large variations in its orientation, size, and texture, but within wide limits such variations do not usually prevent efficient recognition. The present study is directed towards the following questions. Will normal monkeys also show the ability to identify transforms of objects, even on the first occasion on which they are presented with a particular transform in their entire history? Regardless of whether or not such an identification requires practice, what are the brain regions that appear to be especially involved in allowing transforms of objects to be recognized? Are such regions separable from those that are involved in the initial acquisition of a meaningful object to the animal's repertoire?

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In human patients, Warrington and her colleagues (Warrington and Taylor, 1973, 1978; Warrington, 1982) have argued that there is a categorical stage of perception in which the representation of a 'prototype' of an object is achieved, and that localized lesions can interfere with the ability of patients to identify 'unusual views' of common objects. At a further stage of categorization, representations of objects, having already achieved prototypical status, can acquire meaning. The current study is aimed towards seeing whether similar stages might also exist in the monkey, and to suggest where their neural substrates may lie.

The methods used here to test the response of monkeys to transforms of objects gradually evolved over a period of a few years, starting in 1969. The current study reports only the methods finally adopted, although the first group of animals had also been involved in the development stages. The second group of animals had no prior experience with formal visual discriminations except that recorded below. The general strategy used was the same throughout. The animals were first taught a visual discrimination in which a rewarded object was paired with an unrewarded object that was shown for only a single trial. Thus there was never a constant negative object: a new negative object occurred on every trial, whereas the positive object remained constant and unchanged during the whole of the discrimination learning phase. After the discrimination was mastered, the same task continued but, randomly and relatively infrequently, transforms of the positive object were inserted as 'probe trials'. As there was never a constant negative stimulus, the problem of having to transform the negative object by an equivalent amount as the positive object was at least partially circumvented although, as will be seen, there are still methodological issues that remain.

In addition to this principal strategy, of which as will be seen there were two alternative forms, other tasks were also studied, especially selection of already acquired meaningful objects (namely, food objects), tests of positional generalization, and a measure of the sensory capacity for fine discriminations between objects.

MATERIAL

The animals used were Rhesus monkeys (*Macaca mulatta*). Two sets of animals were studied at different times; they contained overlapping but different lesion subgroups. Set A consisted of monkeys with lesions of parietal cortex (n = 4), prestriate cortex (n = 3), or inferotemporal cortex (n = 4). These animals had participated in two pilot studies, some of the testing having been given preoperatively, from which the final methods of testing visual transforms evolved for the study reported here. Set B consisted of monkeys with lesions of the anterior inferotemporal cortex, prestriate cortex, or the fundus of the superior temporal sulcus; there was also an unoperated control group (n = 3 in each group). These animals had no formal training on visual transforms other than that reported here. They also had been taught a pattern discrimination between a 'plus' and a 'square', on which they were retested two weeks postoperatively (*see* Section II), and then proceeded directly to the transform study. At the time of surgery Set A animals ranged in weight between 4.5 and 6 kg, and Set B between 5 and 9 kg. They were maintained on a daily food schedule of chow, fruit, and vitamin supplements that supported normal growth and health.

SURGICAL AND HISTOLOGICAL PROCEDURES

Lesions were placed in one stage under aseptic conditions using standard techniques for cortical resections in the monkey. The animals appeared normal in their everyday behaviour, and there were no signs of any visual disturbances. On completion of testing the monkeys were killed with an overdose of anaesthetic and perfused transcardially with saline followed by 10 per cent formol-saline solution. Histological preparations were slightly different for the two sets of animals. Set A brains were cut on a freezing microtome, sectioned at 50 μm and every tenth section through the lesion site was stained with thionin. Set B brains were embedded in celloidin, sectioned at 50 μm and every tenth section through the lesion site was stained with cresyl violet.

HISTOLOGICAL OBSERVATIONS

Reconstructions of the lesions are shown in fig. 1A to F. The lesions are drawn on standard views of the macaque brain, together with drawings of actual cross-sections through the lesions. The lesions were on the whole placed appropriately as intended. The more detailed histological findings are as follows.

Set A

Inferotemporal lesions. The intended lesion site corresponded roughly with area TE of von Bonin and Bailey (1947), called 'inferotemporal' by Cowey and Gross (1970) and 'anterior inferotemporal' by Mishkin (1972). In most cases the lesions were as intended, with removal of a substantial portion of the inferior temporal cortex. In one monkey (No. 91), however, the ablation was substantially smaller, its anterior limit being 4 to 5 mm more posterior than in the other 3 monkeys.

Damage to tissue outside the intended lesion was present in most cases. Only in Monkey 91 was the lesion entirely restricted to the inferior temporal cortex and the underlying white matter. Damage outside area TE occurred in the superior bank of the superior temporal sulcus (*sts*) and was common to the region (area TF) medial to the occipital temporal sulcus (*ots*). In 2 cases the lesion also extended deeper through the temporal white matter, invading subcortical or medial temporal structures. Monkey 97 sustained unilateral damage to the tail of the caudate nucleus and to a small portion of the lateral geniculate nucleus (outer 2–3 parvocellular layers, parafoveal projection region, *see* Malpeli and Baker, 1975). In the other monkey (No. 95) there was bilateral damage to the hippocampal complex.

Prestriate lesions. The prestriate lesion was intended to correspond to the 'foveal prestriate' lesion of Cowey and Gross (1970) and the 'posterior inferotemporal' lesion of Mishkin (1972), the limit of which extends rostrally approximately 1 cm in front of the inferior occipital sulcus (*ios*), superiorly to the level where the sylvian and *sts* sulci appear to join, and bounded ventrally by *ots*. The caudal bank of the *sts*, the rostral bank of the lunate sulcus (*ls*), both banks of the uppermost part of the *ios* and the lateral banks of *ots* were intended to be included in the lesion.

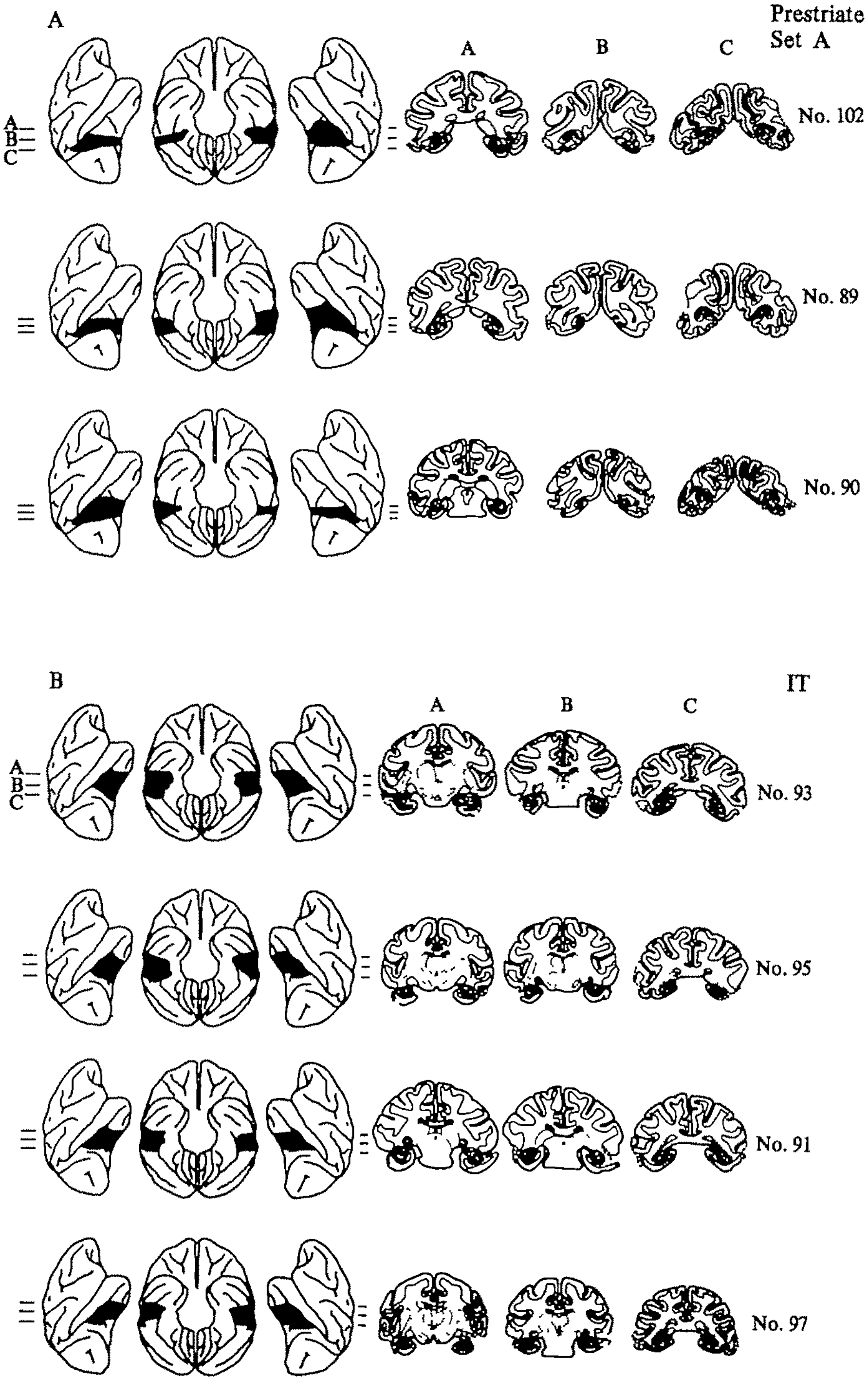
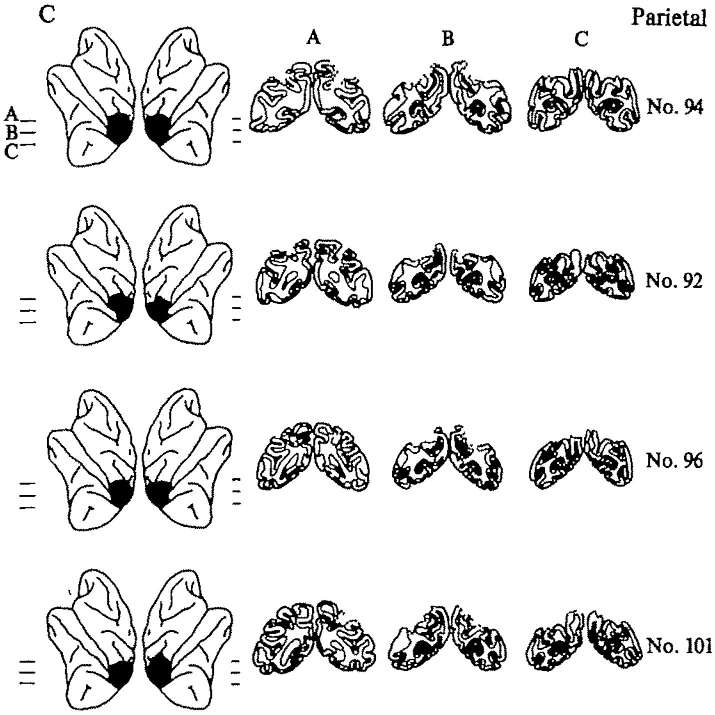


FIG. 1A–F. Reconstructions of lesions.


C
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A
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B
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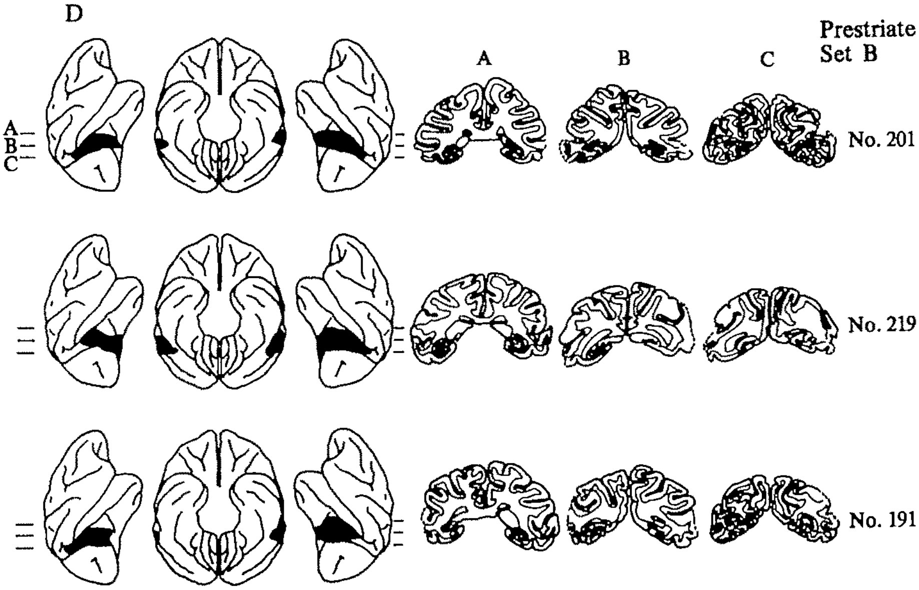
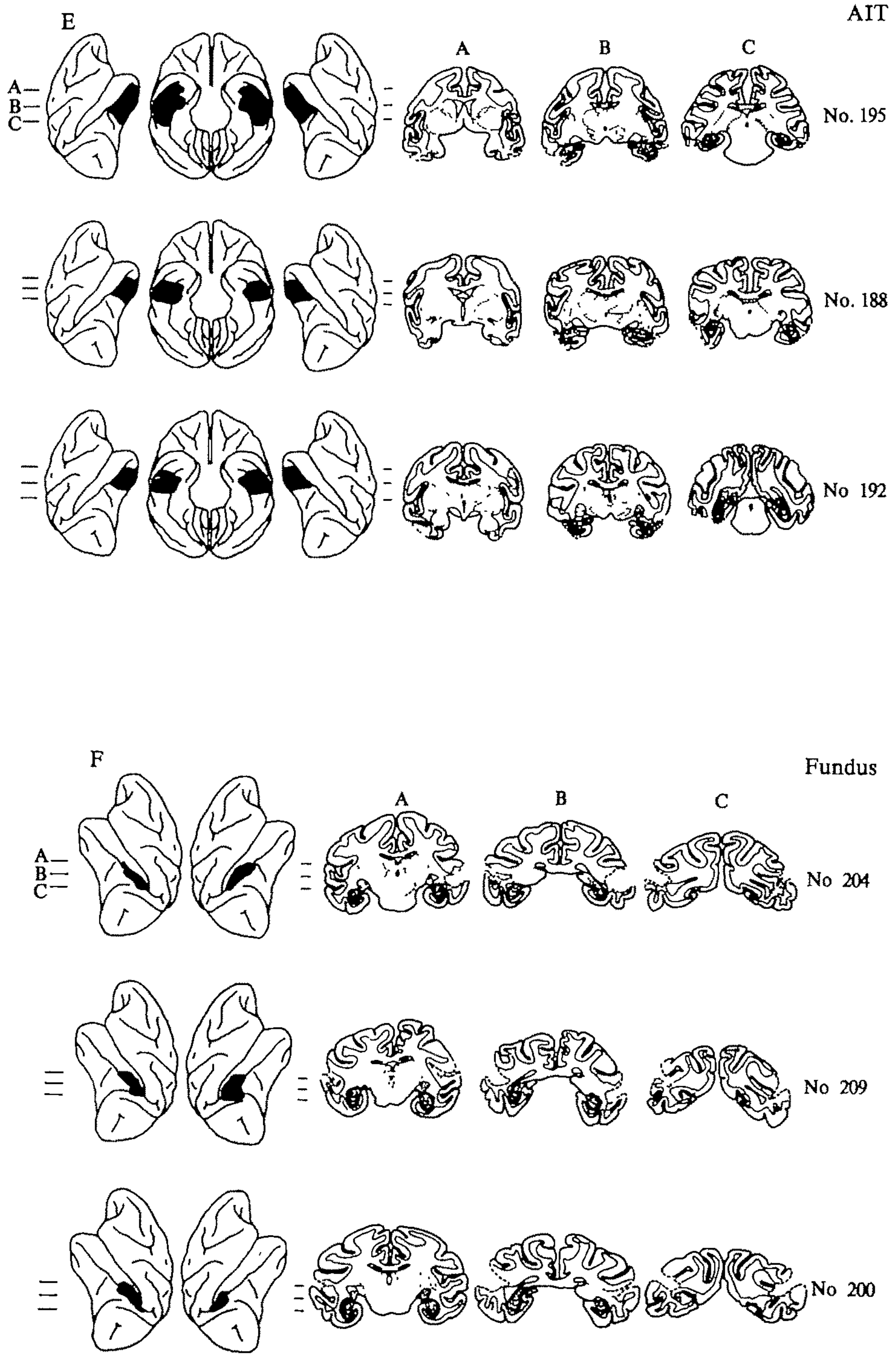

D
Prestriate
Set B
A
B
C
A
B
C
No. 201
No. 219
No. 191


E
AIT
A
B
C
A—
B—
C—
No. 195
No. 188
No 192
F
Fundus
A
B
C
A—
B—
C—
No 204
No 209
No 200

The lesions were roughly as intended although in nearly every animal (Monkey 89, right hemisphere, being an exception) the limit of the lesion was less than 10 mm anterior to the *ios*. In 2 animals (Nos. 90 and 102) the lesion extended ventromedially beyond the *ots* and also slightly caudally to include the posterior bank of *ls*. The lesions in these same 2 animals were substantially larger in the left hemisphere than the right.

Parietal lesions. The parietal lesion was intended to extend from *ls* (not including the rostral bank) forward to the postcentral dimple, inferiorly to the highest level of the sylvian fissure and dorsomedially to the midline. It was intended to include the depths of the intraparietal sulcus (*ips*). The rostral boundary arched from the *ips* in an anterodorsal direction to the postcentral dimple. The bulk of the intended lesion fell in area 7.

Although the parietal lesions varied slightly, they were all roughly as intended. In one case (No. 101) the lesion did not quite reach the midline; in contrast, in another monkey (No. 92) the lesion extended into the cingulate sulcus on the medial surface. In all 4 monkeys the ablation did not reach the depths of the *ips*. Finally, in 3 animals (Nos. 96, 92, 94) the lesion invaded the superior limb of the fundus with *sts*.

Set B

Anterior inferotemporal lesions. The lesion was intended to extend rostrally from approximately 1 cm anterior to the *ios* to the inferior temporal pole. The lower bank of *sts* was also to be removed. Posteriorly, the lesion overlapped extensively with the inferior temporal lesion in Set A animals, but the anterior inferotemporal lesions extended considerably further anteriorly.

In each case the ablations were very much as intended, although they did not extend to the pole. The posterior limit in one monkey (No. 188) fell approximately 1.4 to 1.5 cm rostral to the *ios*, 4 to 5 mm anterior to that in the other 2 monkeys. In one monkey (No. 195), left hemisphere only, there was some invasion of the hippocampus, damaging CA1 and the subiculum.

Prestriate lesions. These were intended to be the same as in Set A. The lesions in 3 monkeys (Nos. 191, 201, 219) were smaller than in Set A. As in the case of the Set A prestriate group, the lesion did not extend as far anteriorly as planned, but also in the present group all lesions fell considerably short of the ventral limit, the *ots*. This was most extreme in Monkey 191, right hemisphere (*see* fig. 1D).

Fundus lesions. As intended, the lesions extended in *sts* rostrally 9 to 12 mm from the junction of the sylvian fissure and *sts*. Both superior and inferior banks of the *sts* were removed. In each case there was some bilateral sparing of the superior limb of the fundus. Cortical damage to tissue bordering either side of *sts* was also common.

I. VISUAL TRANSFORMS

Methods

In all tests, the animals were first given a two-choice discrimination between an invariant positive stimulus and a different negative object, 30 trials per day, until a criterion of 90 out of 100 correct trials was achieved. The objects were a miscellaneous variety of objects from the laboratory inventory, except that the positive and negative stimuli were always painted with the same colour. After the animal reached criterion, it was then given probe tests with transforms in one of two paradigms.

(1) Two-choice transfer paradigm. The animal continued to have a choice between the constant positive and a new negative in every trial. In each block of 30 daily trials, 6 trials were inserted in which the positive object was transformed. Two of these were of orientation, 2 of size, and 2 of lighting/shadow configuration. The orientation transforms were typically of 90 deg rotation, the particular rotation chosen so as to appear recognizable to a human observer, that is, head-on views with radical foreshortening were avoided. Of the size transforms, one was to a bigger and the other to a smaller size of the same object. The lighting transform was produced by turning off the central overhead lamp in the test compartment and turning on a sidelamp either to the right or to the left and above the objects (*see* fig. 2). The location of the lamps is described in the Apparatus section. An attempt was made, as described above, to choose negative objects on the transform 'probe trials' that were approximately the same size and with the same orientation as the major axis of the positive transform. Only the positive transform was rewarded. The description of all orientation and size transforms can be found in the Appendix. Photographs of the objects together with the two orientation and two size transforms for each are shown in fig. 3.

(2) Six-choice transfer paradigm. Because the negative stimulus was made roughly of the same size and orientation as the positive transform there was a possibility that the transform trials were more difficult than the nontransform trials, and hence a deficit might have occurred for this irrelevant reason. An attempt was made to circumvent this by pairing the positive object, whether or not it was transformed, with 5 novel negative stimuli on every trial. The negative stimuli were chosen at random and therefore were likely to include objects of varying size and orientations. The sequence was as follows. After the animal mastered the two-choice learning stage, but before transforms were introduced, it was given further discrimination trials with the positive stimuli in a six-choice situation, with 5 novel negative objects on every trial, until the animal again reached a criterion of 90 out of 100 correct. Then transforms were introduced as above, 6 probe trials in each daily session of 30 trials.

In both paradigms, a daily session was not counted if (rarely) the animal achieved less than 90 per cent correct of the *non*transform trials in that session. Daily sessions were continued until the animal had achieved 10 acceptable sessions.

Set A animals were given 4 two-choice problems and 2 six-choice problems. In Set B, they were given 3 of each. The orders in which these were given were the same for all animals in each set, but differed between sets; they are indicated in the Appendix and fig. 3.

Apparatus. All testing was carried out in a Wisconsin General Test Apparatus. The compartment in which the objects were placed was 84 cm wide, 46 cm deep and 77.5 cm high. Normal illumination consisted of an overhead 60 watt incandescent strip-light, 18 cm long, centrally placed. For the lighting/shadow transform, the overhead lamp was extinguished and either one of two sidelamps was lit. One lamp was mounted vertically on the testing board, 13 cm from the front edge and 4 cm from the right-hand side (from the monkey's viewpoint). The other was positioned horizontally at the extreme left-hand side of the testing compartment, 24 cm above the testing board and 28 cm from the monkey's cage. The lamps were 'Vesta 1E', 40 watts each.

The animal was tested in a transport cage, the front wall of which contained a rectangular 'peep-hole', 10.2 cm wide and 6.4 cm high, with the lower edge 31.3 cm above the floor of the cage. Beneath that was an opening 26.0 cm wide and 6.5 cm high, with the lower edge 20.8 cm above the floor of the

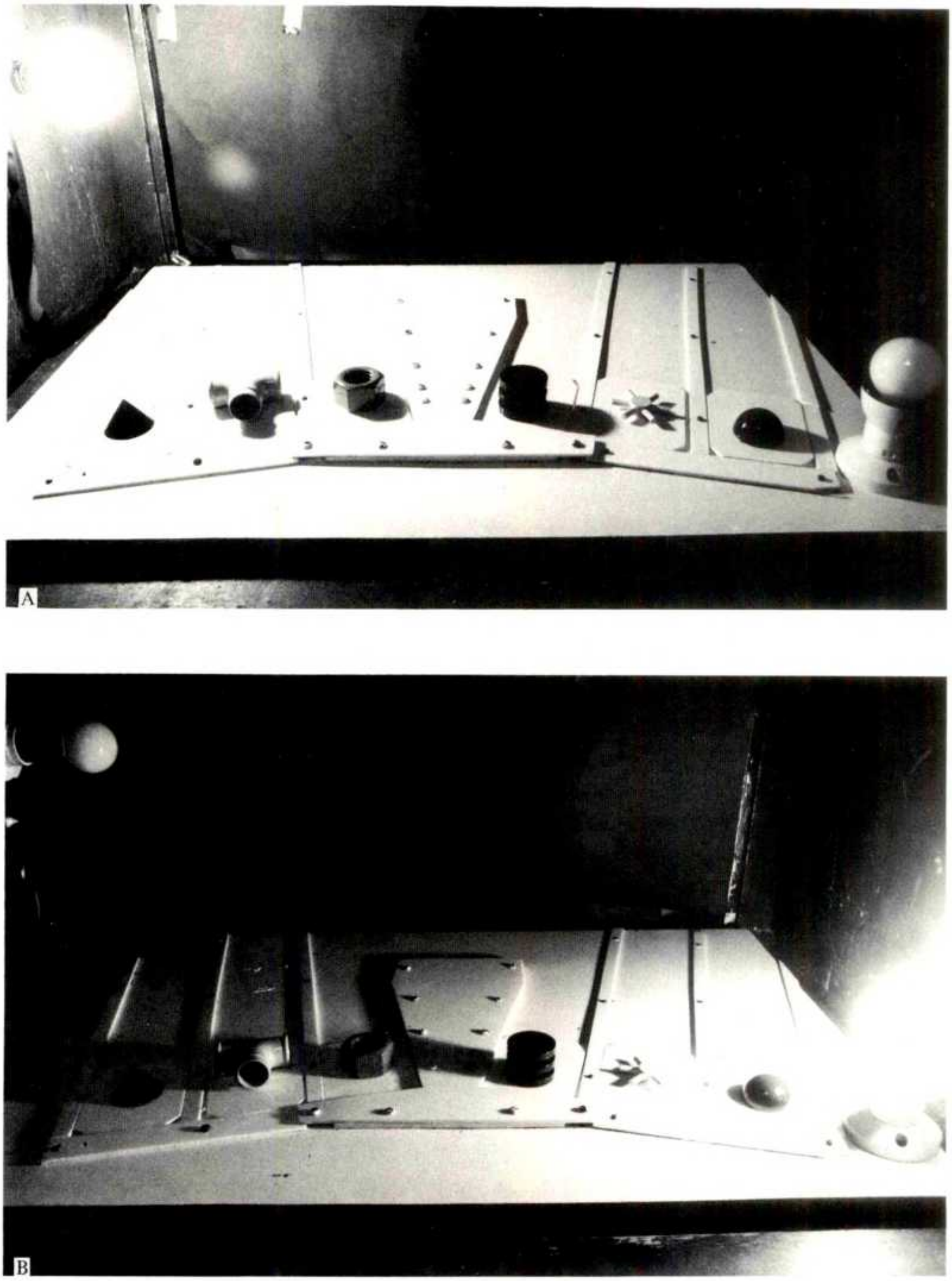


FIG. 2A and B. Photographs of the two shadow transforms, shown with the six-choice apparatus.

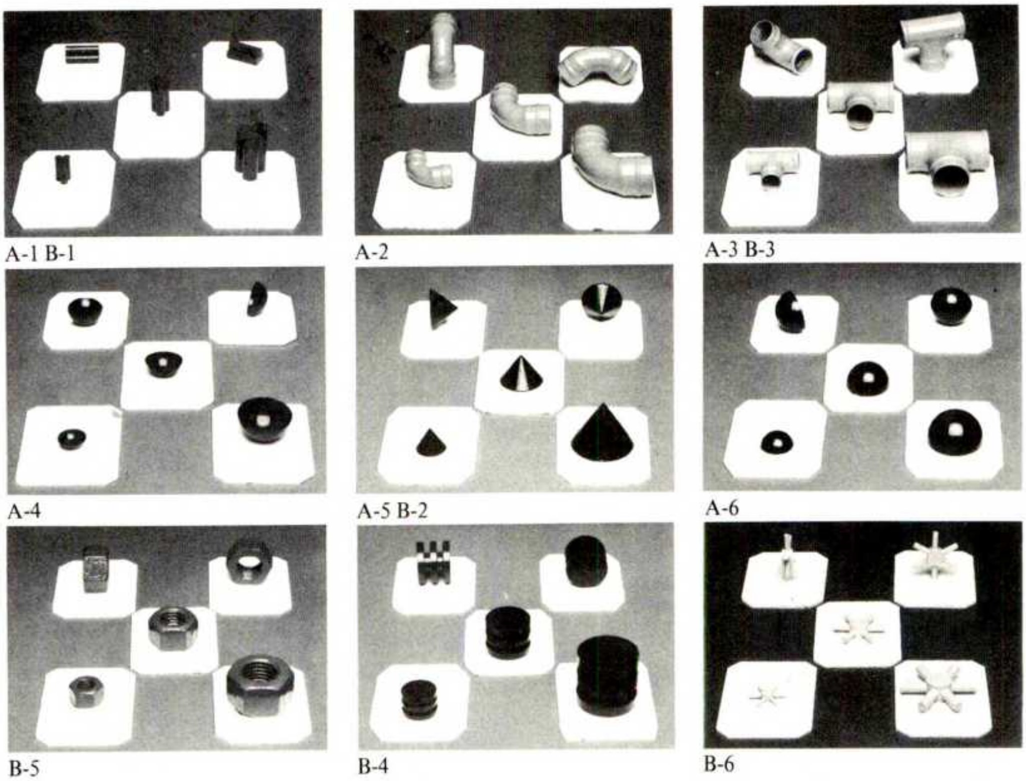


FIG. 3. Photographs of all stimulus objects with size and orientation transforms. View of object in the centre of each panel is of the standard training object. The forward views are of the two size transforms, and the back views are of the two orientation transforms. The label for each panel indicates the order in which the problem was presented to each group (*see* Appendix).

cage, through which the animal could reach an object and retrieve the peanut reward. When the six-choice experiments were introduced, the lower opening was widened to 41.0 cm to enable the animals to reach all the objects. The purpose of this arrangement was to restrict the range of different views the animal could have of the object. The objects were angled in the test compartment towards the peephole (*see* fig. 2). Each object was placed on a movable plastic plaque, approximately 10 × 7.5 cm, which had to be displaced to reveal the food reward underneath. The distance between the centres of the objects in the two-choice arrangement was 12.5 cm. This was also the distance between the 2 middle objects in the six-choice paradigm. The next most peripheral object in the six-choice arrangement was 10.5 cm from each middle one, and the most peripheral object was 7.5 cm from its neighbour. The 2 middle objects were 16.5 cm from the front of the testing board. The screen separating the animal from the test board was lowered immediately after the animal touched one object and, if correct, had retrieved the reward.

Results

Initial learning of objects, prior to transform tests. The inferotemporal groups, especially the anterior inferotemporal animals, were impaired in initial learning of

TABLE 1 SET A ANIMALS MEAN TRIALS TO LEARN (L) AND % TRANSFORM (T)–% NONTRANSFORM (NT) ERRORS (%T–%NT)

Two-choice

	3 Cylinders		*Elbow*		*T-piece*		*Bowl*		*Means*	
	L	*%T–%NT*	*L*	*%T–%NT*	*L*	*%T–%NT*	*L*	*%T–%NT*	*L*	*%T–%NT*
Parietal	32 5	7 08	7 5	4 17	0	2 92	10 0	7 19	12 5	5 34
Prestriate	143 33	40 14	53 33	33 89	0	23 33	126 67	19 72	80 83	29 27
IT	190 0	20 83	86 67	19 58	0	14 31	80 0	27 09	89 17	20 45

Six-choice

	Cone			*Half ball*			*Means*			
	L_2	L_6	*%T–%NT*	L_2	L_6	*%T–%NT*	L_2	L_6	L_{2+6}	*%T–%NT*
Parietal	5 0	2 5	4 98	0 75	0	7 70	2 87	1 25	4 12	6 34
Prestriate	63 3	54 67	25 97	4 67	11 33	23 06	34 0	33 0	67 0	24 52
IT	31 67	130 0	34 17	3 0	33 67	25 97	17 33	81 83	99 16	30 07

the positive objects. The prestriate group was not as severely impaired, on average, as the inferotemporal groups, but was nevertheless worse than the parietal, fundus, and unoperated control groups. The results are set out in Tables 1 and 2 (columns labelled 'L') for each group and for each individual problem, together with the means over all problems. Figs. 4 and 5 summarize the overall results for each set, and fig. 6 the results for both sets combined. These show the expected deficit already known to be associated with inferotemporal lesions.

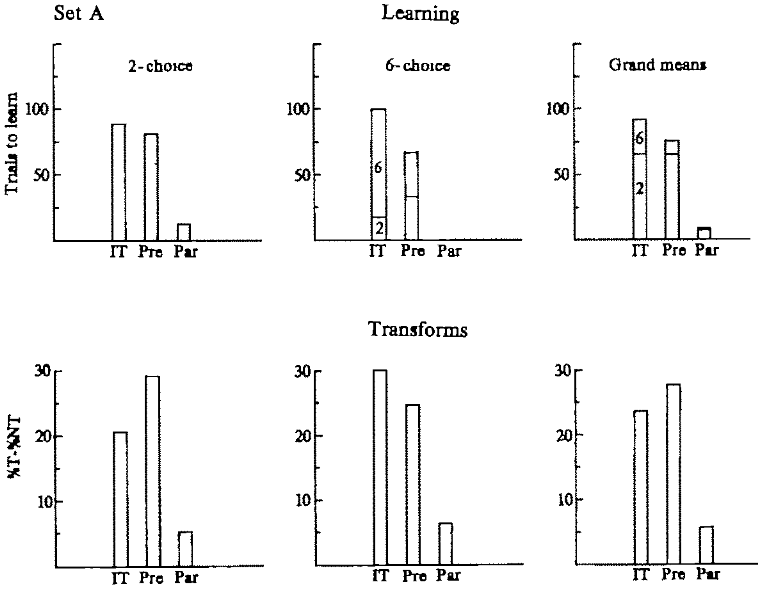


FIG 4. Mean trials to criterion for initial learning, and percentage transform minus percentage nontransform errors for Set A animals. For the six-choice problems, the trials to criterion for initial learning are shown separately for the two-choice and the subsequent six-choice phases ('2' and '6'). Abbreviations as in text

TABLE 2 SET B ANIMALS MEAN TRIALS TO LEARN (L) AND % TRANSFORM (T)–% NONTRANSFORM (NT) ERRORS (%T–%NT)

Two-choice

	3 Cylinders		*T-piece*		*Hex nut*		*Means*	
	L	*%T–%NT*	*L*	*%T–%NT*	*L*	*%T–%NT*	*L*	*%T–%NT*
Unoperated	41 0	16.67	8 33	12 36	18.67	24.31	22.67	17.78
Fundus	69.0	16.25	11 0	8 05	4.67	14 03	28.22	12.78
Prestriate	142 3	20.69	4 67	15 88	24.0	24 58	57.0	20 38
AIT	958.0	38 47	226 0	16 39	0 0	28 13	394.67	27 67

Six-choice

	Cone			*Reel*			*Star*			*Means*			
	L_2	L_6	*%T–%NT*	L_2	L_6	*%T–%NT*	L_2	L_6	*%T–%NT*	L_2	L_6	L_{2+6}	*%T–%NT*
Unoperated	8.0	3 33	16.39	0	19 67	11 11	25.67	22.3	7.64	11.22	15 11	27.33	11.71
Fundus	43 0	3 0	20.97	0	0	7 5	14.33	0	4.17	19 11	1 0	20 11	10 88
Prestriate	30 33	71 33	35 83	0	35 67	20.83	41 0	0 33	20 0	23 78	35 78	59 56	25 55
AIT	721 67	410 0	37 22	32.67	189 33	11.25	146 33	127 0	29 86	300 22	275 44	575 66	26 11

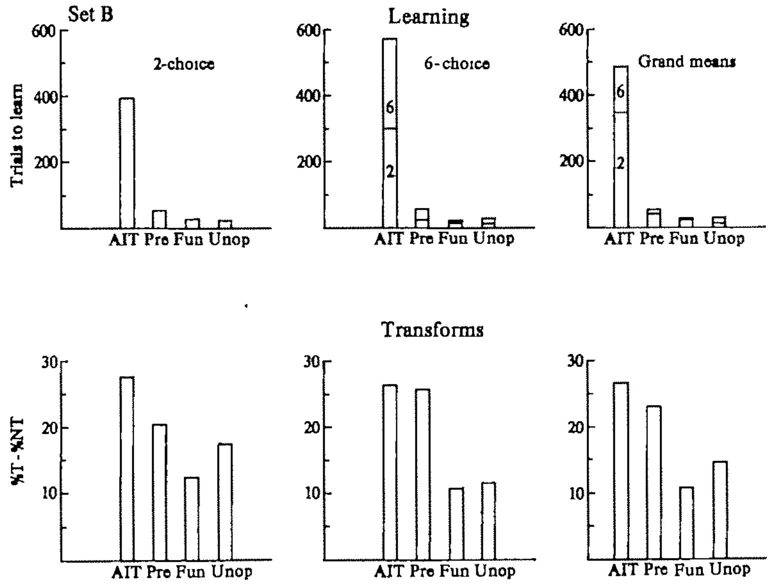


FIG. 5. Same as fig. 4, for Set B animals. Abbreviations as in text.

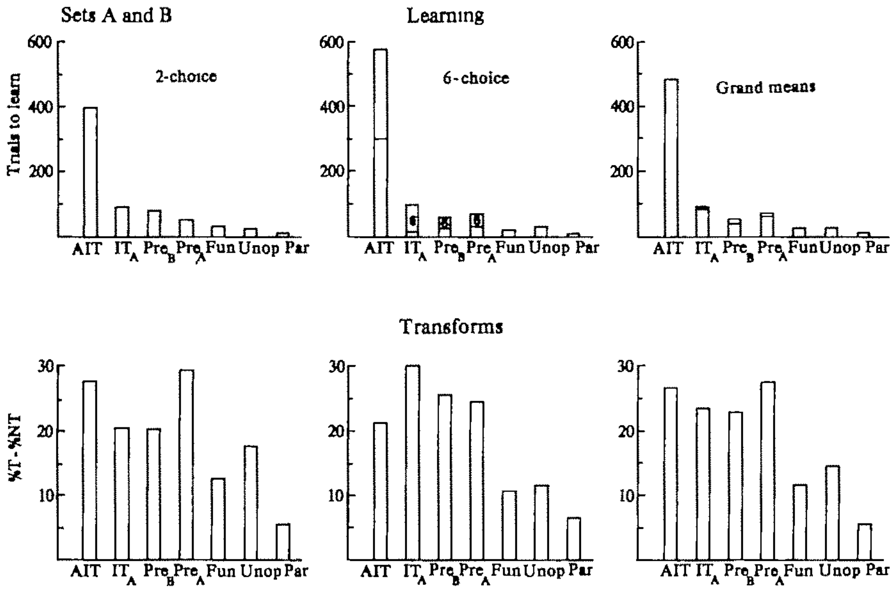


FIG. 6. Data for Sets A and B combined. Abbreviations as in text

The six-choice paradigm involved a second stage of initial learning with 6 alternatives after the animals had mastered the two-stage phase. All animals required further experience to transfer from the two-choice to the six-choice stages. But the performance of the inferotemporal (IT) and anterior inferotemporal (AIT) groups was striking (*see* Tables 1 and 2). The latter, having required 300 trials on average to learn the two-choice phase of the problems, took another 275 trials to master the six-choice phase. The IT group, having mastered the two-choice phase relatively efficiently, then took almost five times as many trials to transfer to the six-choice situation.

One AIT animal in Set B, namely No. 188, showed uncharacteristic initial learning scores. He learned the very first object problem moderately slowly (144 trials), as would be expected of animals in his group (and also very poor pre-post savings of the 'plus *vs* square' problem, *see below*). Thereafter he learned subsequent object problems very quickly, with zero trials to criterion in all but one problem out of the remaining 5, in which he required just 25 trials. (The mean trials to criterion over all problems for the other 2 animals in the group was 507.) It may be relevant that this animal had the smallest lesion in the AIT group, extending less far posteriorly (*see below*).

Another IT animal, No. 97, was so severely impaired in initial learning of objects that he was abandoned after the first problem, which he failed to learn in 600 trials (his score is not included in the calculations). It is of interest that his lesion was somewhat deeper, at least in the right hemisphere, than the others in the group, and included the tail of the caudate nucleus and a small portion of the lateral geniculate nucleus (*see below*).

Transforms. Both the prestriate and the IT groups were impaired, and approximately to the same extent, on the transform 'probe' trials. More than one-quarter of their responses were errors. This compares with a score of 5.8 per cent for the parietal group in the Set A animals, who were more experienced than Set B. In the latter the fundus and normal groups averaged 14.3 per cent. It is interesting that even the normal and fundus groups (which throughout were unimpaired on any test in relation to the other two groups) made appreciable numbers of errors on transform trials, and more than twice as many as the more experienced control animals. The data for transform errors minus nontransform errors (*see below*) are set out in Tables 1 and 2, and figs. 4, 5 and 6.

Type of transform. The pattern of errors on the three different types of transforms was much the same in all groups. More errors were made on orientation transforms than lighting or size. Table 3 summarizes the mean percentage errors (over all problems and all testing days) for each of the three categories of transforms. Results are combined for the 2 shadow (A and B) and the 2 orientation (C and D) variations, but the large (E) and small (F) transforms are plotted separately because of their relevance to the study by Yaginuma *et al.* (1982) (*see below*). This same pattern was discernible, although less strongly, on the first occasion on which transform trials were given on the first day of the first problem (*see* Table 4).

One subsidiary experiment was carried out to determine the rate at which animals would eventually master particular types of transforms to a criterion. After the Set A animals had completely finished with the two-choice 'elbow' problem, including the 10 transform sessions, testing was continued until they reached a 90 per cent

TABLE 3 MEAN PERFORMANCE (PERCENTAGE ERRORS) ON DIFFERENT TRANSFORMS

			Size		
	Shadow (*A*+*B*)	*Orientation* (*C*+*D*)	*Large* (*E*)	*Small* (*F*)	*Overall*
Set A					
Parietal	4.17	8.75	5.83	2.92	5.83
Prestriate	25.28	43.89	23.33	21.11	30.09
IT	18.33	36.67	14.44	32.22	26.02
Set B					
Unoperated	8.31	28.06	9.44	14.44	16.02
Fundus	5.83	25.27	3.89	7.78	12.50
Prestriate	15.56	43.61	18.33	17.78	25.74
AIT	21.11	47.50	16.67	27.78	30.37

criterion on each of the specific transforms. They were given 36 trials daily, consisting of 18 transform trials (3 of each of the 6 transforms), and 18 nontransform trials. As criterion performance was reached on each transform, nontransform objects were substituted to keep the number of daily trials constant. The results are shown in Table 5. The prestriate group as a whole found the size transform (and especially the large one) more difficult than the orientation transform, and the IT group also were only slightly poorer on orientation than size. While orientation was clearly moderately more difficult overall under the conditions of this study, paradoxically size

TABLE 4 TRANSFORM PERFORMANCE ON FIRST TRIALS (PERCENTAGE ERRORS)

			Size		
	Shadow (*A*+*B*)	*Orientation* (*C*+*D*)	*Large* (*E*)	*Small* (*F*)	*Overall*
Set A					
Parietal	6.25	10.42	4.17	0	6.25
Prestriate	19.44	38.89	38.89	11.11	27.78
IT	27.78	38.89	11.11	44.44	31.48
Set B					
Unoperated	11.11	36.11	27.78	27.78	25.00
Fundus	11.11	33.33	11.11	5.56	17.59
Prestriate	22.22	33.33	16.67	33.33	26.85
AIT	16.67	55.56	22.22	44.44	33.33

appears to have caused relatively more difficulty in showing improvement with practice.

Nontransform trials. These were required to contain less than 10 per cent errors in each daily session (*see above*). But, within those limits, the IT and prestriate groups nevertheless performed more poorly on the nontransform trials than the other groups. The results are shown in Table 6, which shows that these two groups made between 3.15 and 1.85 per cent errors, whereas the other groups made only between 1.28 and 0.16 per cent errors. It is also the case that more daily sessions had to be discarded for these two groups than for any others: 8 sessions for the AIT animals of Set B (to achieve a total of 180 acceptable sessions over all problems) and 7 for the prestriate animals of both sets combined (to reach a total of 360 acceptable sessions). None of the other groups, including the IT animals of Set A, required any extra sessions because of an excess number of nontransform errors.

One animal in the prestriate group in Set A, namely No. 89, appeared to fall well outside the level of performance of other prestriate animals in terms of his high error rate on nontransform trials. He also required many more trials, on average, by a factor of at least 5 to relearn the six-choice problems immediately after they had been learned as two-choice problems, which themselves had been learned at a slower rate by him than by other animals. (On the transform trials, however, he fell in the middle of the range of the prestriate group of the set.) There were no detectable features of the histological reconstruction of the lesion that differentiated this animal from the others in the set.

Transform vs *nontransform scores.* As the nontransform scores indicate that the IT and prestriate groups were more likely to make errors on the baseline discrimination itself, their excessive number of transform errors must be judged against that baseline level. That is, one must consider whether the transform impairment merely reflected a more general and nonspecific discrimination performance difficulty. This issue was addressed in three different ways.

(1) Perfect nontransform performance as baseline. One way to see whether the nontransform level mattered is to eliminate it by only using those daily sessions in which no nontransform errors were made (*see* Table 6, last column). When this is done, the difference between prestriate and temporal lobe groups, on the one hand, and all other groups in each set still remains. In Set A, there is no overlap between the percentage transform errors between parietal lobe and the other two groups on any of the six problems, despite the reduction in the amount of data available ($U = 0$, $P = 0.005$ for the difference between mean scores of individual animals). In Set B, a similar pattern emerges except for one overlap between the unoperated controls and the prestriate animals on one out of the six problems. There is no overlap between the prestriate or AIT groups and the fundus group. If the fundus and unoperated groups are combined, as these two control groups are not themselves different from each other, even the single case of overlap of group means disappears. (The difference between the mean scores of individual animals in the fundus and unoperated groups and the other two groups is significant by Mann-Whitney test, $U = 2$, $P = 0.004$.) It is also interesting to compare these results with the overall data in which all nontransform days are included. With these data, there is no overlap

TABLE 5 SET A. LEARNING SCORES FOR EACH TRANSFORM PROBLEM (NO OF ERRORS TO CRITERION OF 9/10, EXCLUDING LAST 10 TRIALS)

		Shadow	*Orientation*		*Size*	
		$A+B$	C	D	*Large*	*Small*
Parietal						
94		0	0	0	0	0
92		0	0	0	0	0
96		0	0	0	0	0
101		0	0	0	0	0
	Total	0	0	0	0	0
Prestriate						
102		0	0	8	14	0
89		6	2	0	11	11
90		3	0	9	6	0
	Total	9	2	17	31	11
IT						
93		0	1	7	6	3
95		0	1	8	9	0
91		1	1	6	2	0
	Total	1	3	21	17	3

TABLE 6 PERFORMANCE ON TRANSFORM AND NONTRANSFORM TRIALS (PERCENTAGE ERRORS)

	Mean %T	*Mean %NT*	*Mean (%T−%NT)*	*Mean %T when NT = 0*
Set A				
Parietal	5.83	0.16	5.67	5.68
Prestriate	30.09	2.43	27 68	27.26
IT	26.02	2.26	23.66	23.08
Set B				
Unoperated	16.02	1.28	14.75	16.13
Fundus	12.50	0.67	11.83	11.23
Prestriate	25.74	1.85	22.96	23.35
AIT	30.37	3.15	26.89	25.09

between any of the prestriate or temporal lobe groups and any of the other groups on even a single problem. Not surprisingly, the overall performance for transforms is slightly worse compared with those selected days in which performance on nontransforms is perfect, but the difference is small: the mean difference in performance on transforms between the two sets of data is only 3.4 per cent for the prestriate and IT groups, a negligible difference (*see* Table 6).

(2) Another approach is to see how much of the variance in transform trial performance can be accounted for in terms of nontransform performance, that is to examine the statistical relationship, if any, between the incidence of nontransform and transform performance in individual animals. An appropriate method of analysis is multiple regression. When this is done, the amount of variance accounted for in the transform scores by the regression of transforms onto nontransforms lies between 0 and 9.1 per cent (*see* Table 7). (For the regression analysis all raw data were transformed into log values to normalize the distributions, but the percentages of variances that emerged with raw untransformed scores were of the same order of magnitude.) That there should be some relationship, of course, is not surprising, because a decrease in reward rate during nontransform trials is apt to have its effects on all trials in the session, and all animals have their 'on' days and 'off' days which will affect performance nonspecifically. The effect is significant for the prestriate group of Set A but not for that group in Set B; it is also significant for the AIT and fundus groups of Set B, but not for the IT group of Set A. It is obviously too small to account for the major deficits in the prestriate and temporal lobe groups: more than 90 per cent of the variance in the transform trials must be accounted for in other terms and, as we have seen, even when the nontransform variance is completely removed, the deficits still remain.

TABLE 7. REGRESSION ANALYSIS

	Percentage variance of transform scores accounted for by nontransform scores	*Regression coefficient*
Set A		
Parietal	1.11	0.19 (n.s.)
Prestriate	9.11	0.33*
IT	1.71	0.14 (n.s.)
Set B		
Unoperated	0	0.11 (n.s.)
Fundus	2.91	0.16*
Prestriate	1.82	0.17 (n.s.)
AIT	3.59	0.21*

* $P < 0.01$.

(3) Weighted transform-nontransform scores. The question still remains as to how to put the transform scores into a quantitative form that meaningfully takes the nontransform baseline level into account. There is a difficulty in using a relative measure because the nontransform levels for all groups are very near to baseline, and a ratio shows large fluctuations with relatively small changes in the nontransform absolute values.

A measure that appears to have the advantages of adequate sensitivity and of simplicity is the percentage nontransform errors (of total nontransform trials) minus the percentage transform errors (of total transform trials). These were calculated for each problem and each animal, and the group means for each problem can be seen in Tables 1 and 2, and are also summarized for all problems in figs. 3, 4 and 5. The pattern that emerges is that both the prestriate and IT groups have a larger residue of transform errors than the other groups, but are approximately equal to each other. Indeed, there is no overlap between the means of the prestriate and IT groups and the other groups in either set on any single problem.

Therefore, considering the initial learning in relation to performance on transform trials, the picture that emerges is that the prestriate group is disproportionately bad at transforms in relation to how quickly it could master the original problem. That is, the AIT group took much longer, as expected, to learn the initial problems, but was no worse than the prestriate group at transforms once criterion was achieved.

One AIT animal, No. 188, who had already shown uncharacteristically rapid initial learning after the first problem, also showed relatively fewer nontransform errors than other temporal lobe animals. Its weighted transform error score also declined after the first problem. Its lesion was the smallest in its group, with its posterior limit some 3 or 4 mm anterior to the others. Animals 191 and 219 in the prestriate group of Set B were approximately matched in terms of initial learning scores, but 219 was considerably more impaired on transform trials. The lesion in the latter animal also extended more ventrally into the posterior inferotemporal region. The lesion in Monkey 191 was the smallest in the prestriate group of its set, especially in terms of not invading area TE, and this animal had the smallest transform deficit in its group. Among the IT animals of Set A, No. 91 had the smallest transform deficit in its group and also the least extensive IT lesion. No. 97 was very severely impaired on initial learning (and food board, *see below*), and its lesion was also relatively extensive and deep.

Practice and response to transforms. Two different questions arise concerning the possible effects of practice: first, whether animals benefit from general experience with a large set of transforms in identifying yet another example of a transform, that is, whether they learn to perceive transforms as a class better with practice and, secondly, whether their proficiency, regardless of the possibility of whether or not it develops gradually with practice, is displayed immediately when any particular transform trial is presented, or whether more than a single exposure of any particular transform is required to make a correct identification. That is, the two questions concern learning *between* the different transform problems, and learning *within* any particular transform problem. In fact, the evidence, taken as a whole, does not support practice in either sense as being important. As regards the first question, Set A animals were somewhat more experienced than Set B, but the only lesion group that was common to both sets, the prestriate animals, showed roughly comparable performance on transform trials, and if anything the Set B prestriate animals were marginally better than those of Set A. On the other hand, the two control groups in Set B namely, the unoperated and the fundus animals, were appreciably worse than the 'control' group in Set A, namely the parietal group (*see* Tables 3 and 6). Nevertheless, it cannot be concluded that the parietal group was necessarily comparable to a 'neutral' control group; an argument could be advanced as to why the parietal group, known to be defective on spatial discriminations (Mishkin, 1972) might be over-dependent on shape cues, and hence better than other controls on transforms. There is, for example, a report that in man parietal lesions might give rise to 'over-constancy' for size perception (Wyke, 1960). There was a tendency for animals in both sets to show some improvement in their weighted transform scores from their first to their last six-choice problem, although not with complete consistency (e.g., the AIT and parietal animals were poorer on their last problem than on the next to the last), and no such trend could be discerned at all with the two-choice problems.

As regards practice *within* problems, it would not be surprising if improvement were seen as the animals were differentially rewarded for responding to the transformed objects, and hence could simply have been learning new objects. Fig. 7 shows the data for each group during each pair of days within all problems, and it will be seen that the separation between prestriate and IT animals and all others is maintained throughout. The data are plotted by pairs of days for visual convenience; the same pattern emerges on a day-to-day basis, and the separation between the AIT, IT and prestriate groups and the others is present on day 1, although somewhat reduced by virtue of poorer performance by the unoperated controls, who averaged 25.0 per cent errors. The amount of improvement between days 1 and 10 within problems for the impaired groups of both sets is slightly less than that of the unimpaired groups (4.63% *vs* 8.49%). On average, the animals of Set B, and especially the unoperated control group (15.74%) showed somewhat more improvement within problems than Set A animals (8.33% *vs* 3.55%). Hence, it is possible that what the greater experience of Set A animals achieved was actually to make them appreciate more quickly than the Set B animals that transforms were going to be a repeating feature of each problem, and therefore to treat the first occasion as a reliable guide for future occasions.

Regardless of the effects of practice within or between problems, one point that emerges strongly is that on the very first occasions on which transforms were presented the control animals showed strong positive transfer. Had they treated the transforms as new objects, they would have been expected to perform at 50 per cent in the two-choice situation and at 16.7 per cent in the six-choice situation on the very first occasions when they saw the transformed objects. The poorest performance amongst control groups was 70.4 per cent on two-choice problems and 79.6 per cent on the six-choice problems. The best performance was highly impressive. Thus the

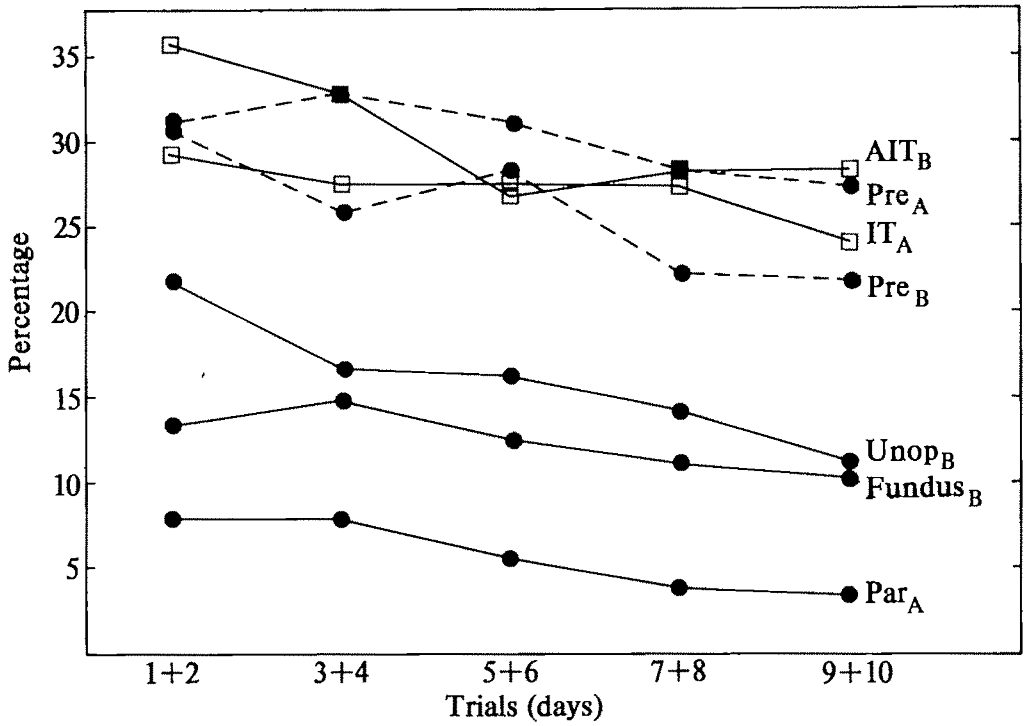


FIG 7. Mean percentage transform minus percentage nontransform errors as a function of trials within all problems for each group. Abbreviations as in text.

parietal group performed on average at 94.8 per cent on the very first occasions they were confronted with transforms. This is despite the fact that animals had consistently not been rewarded for responding to negative objects, and hence there were inbuilt pressures in favour of rejecting the transforms on the first occasions. This might account for why the more experienced control animals in Set A did not show very much within-problem improvement of transform performance: they might have learned already to reject novelty of orientation, size, or shadow arrangement as irrelevant forms of novelty. It should be stressed that this impressive level of positive transfer was to a retinal configuration that in no case had ever been presented to the animal in its entire existence.

The level of performance of the prestriate and IT groups on the very first occasions was, of course, less impressive than that of controls but was nevertheless significantly better than chance in all instances. The nearest any group came to chance level was the AIT group with two-choice problems; they performed at 70.4 per cent, with a chance expectation of 50 per cent.

II. PRE-POST SAVINGS FOR PATTERN DISCRIMINATION

Methods

Animals in Set B were taught a two-dimensional pattern discrimination between a '+' and a 'square' just prior to operation, and eight days following operation. The discrimination was carried out in the same Wisconsin Apparatus as above. The stimuli were formed by black plastic tape on a white plaque 10 × 8 cm. The width of the tape for the + was 2.4 cm and for the square it was 1.2 cm. The length of each arm of the + was 6.0 cm, which was also the outer dimension of each side of the square. The plaques were in runners, and could be pushed away by the animal to reveal the food well. The centres of the plaques were 30 cm apart.

Animals were trained, with peanut reward, for 30 trials per day, until they achieved a score of at least 90 correct out of 100 successive trials. Half of the animals had + positive, the other half square positive. Their assignment to a surgical group was based on making each group approximately equivalent for preoperative trials to criterion.

Postoperatively the same procedure was followed, each animal being retrained with the same positive stimulus as had been used preoperatively.

Results

The pre- and postoperative trials and errors to criterion are shown in Table 8, together with a conventional index of their percentage savings score. This was calculated as follows:

$$\frac{\text{Pre}-\text{Post}}{\text{Pre}+\text{Post}} \times 100.$$

The savings score can vary from +100 per cent (perfect savings) through zero savings to −100 per cent negative savings.

It will be seen that the normal control animals showed high positive savings, the fundus group moderate positive savings. The foveal prestriate group was close to zero savings, and the AIT group showed strongly negative savings, that is, they took longer to learn postoperatively than they had done preoperatively. The findings are consistent with other evidence that the integrity of the anterior region of the inferotemporal region is more important for visual discrimination learning (Iwai and Mishkin, 1968; Cowey and Gross, 1970) than any other posteriorly placed region of association cortex. The fact that savings scores were so poor in this group is also consistent with a view that this region of the temporal lobe is important for the new storage as well as the retention of visually presented forms.

III. FOOD BOARD TESTS

The transform tests just described depend upon the acquisition of previously neutral objects, which then no longer play any important part in the animal's repertoire. A test of the adequacy of storage of visual prototypes that comes closer to the clinical situation is one in which the objects are highly familiar and continue to have important meaning for the animal. For this reason, on frequent occasions we presented both sets of animals with choices of familiar small samples of food placed among an array of nonfood objects.

Methods

Testing was carried out in the Wisconsin Apparatus. A plywood board 47 × 26.7 cm contained 18 wells, each 4.4 cm in diameter. These were arranged in a rectangular grid of 3 rows and 6 columns. The board was tilted at an angle of 15 deg towards the animal. The same array of objects appeared mirror symmetrically on the left- and right-hand sides of the board. On each side were 7 nonfood objects of varying shapes and textures. In one of the 2 remaining wells was a peanut and in the other a small piece of mashed chow, both of which were part of the animals' staple daily diet.

The animals were tested at intervals of two weeks. Set A received 10 such fortnightly tests with one assortment of nonfood objects (Food Board I) and another 10 tests with a new set of nonfood objects (Food Board II). Set B animals received 10 tests with Food Board II followed by 10 with Food Board I. The position of all the objects was changed on every test. The nonfood objects used in Food Board I were a heel tip, new penny, small ball of paper, elastic band, cable clip, hexagonal nut and a circular shelf support. In Food Board II they were a different cable clip, small bulb, another heel tip, tag end, wing nut, halfpenny and a bolt.

The animal was allowed as long a time as needed to find all 4 food objects. Every nonfood object touched or picked up before finding all the food was recorded as an error.

TABLE 8 PATTERN DISCRIMINATION ('PLUS' *vs* 'SQUARE') PRE-POST SAVINGS

	Pre Trials to criterion	*Post*		*% savings*
Unoperated				
205	134(53)*	0(0)		+100.0
210	59(26)	0(0)		+100.0
203	270(104)	59(20)		+64.13
			Mean =	+88.04%
Fundus				
204	132(60)	147(66)		−5.38
209	89(36)	24(10)		+57.52
200	122(51)	42(14)		+48.78
			Mean =	+33.64%
Prestriate				
201	86(39)	114(46)		−14.00
219	82(40)	68(23)		+9.33
191	210(64)	147(52)		+17.65
			Mean =	+4.33%
AIT				
195	210(65)	559(241)		−45.38
188	62(30)	745(276)		−84.63
192	148(59)	277(124)		−30.35
			Mean =	−53.45%

* No. of errors bracketed.

Results

These are presented in Table 9. In both sets of animals it will be seen that the IT animals made, on average, at least 8 times as many errors as the parietal, fundus or normal control groups. The prestriate group's scores fell between those of the control group and the IT animals. The error rates were generally slightly lower in the second series of 10 tests than the first, irrespective of which board was first, but the general pattern of results over both was sustained throughout the whole sequence of 20 tests. In Set A, the difference between the IT and the parietal groups is significant ($U = 0$, $P = 0.01$), as is the difference between the prestriate and parietal groups ($U = 0$, $P = 0.028$). The difference between the IT and prestriate groups is almost significant ($U = 1$, $P = 0.057$). In Set B, the difference between the AIT and the unoperated groups is significant at $P = 0.05$. If the fundus and unoperated groups are combined, the difference between them and the AIT group is significant at the $P = 0.012$ level ($U = 0$). However, the prestriate group is not significant from the combined unoperated + fundus groups ($P = 0.36$). IT animal No. 97, who had been severely impaired in the initial learning of objects, was also the most impaired animal in the food board test. Thus, the IT animals' impairment apparently is not restricted to the introduction of new objects into their repertoire, but extends beyond that stage in sustaining a level of correct selection from that repertoire.

IV. RESPONSES TO OBJECTS AS A FUNCTION OF POSITION

Both the six-choice transform problems and the food board tests required the animals to select objects from a variety of positions, and the former to do so over a wide field. It was of interest to determine, therefore, whether these features as such introduced errors that confounded the overall error rates. The food board and the six-choice tests could be analysed in terms of errors made by animals for each position in the apparatus. In addition two brief experiments were carried out in which the number of objects in the discrimination was restricted to 2, but their locations varied randomly over 6 positions.

Methods

Set A animals, after having received their first six-choice problem and one intermediate problem (cone discrimination, *see below*) were trained on a two-choice task with the stimuli in the central 2 loci in the six-choice testing board (*see* fig. 2). The 4 outer positions were covered with blank white plaques. The positive stimulus was a reel of the form normally used to hold cotton thread. It was 3.8 cm in outer diameter and 3 cm high, with an inner diameter of 2 cm; its main axis was in a vertical orientation. This object was deliberately chosen because the form of the retinal configuration would remain invariant over all positions on the testing board, assuming the animal fixated it in all locations. The negative stimulus changed on every trial. After the animals reached a criterion of 90 out of 100 successive trials correct, the position of the positive stimulus was moved randomly from trial to trial, as was the position of the single negative stimulus. The other 4 positions remained covered by blank white plaques. The only constraints introduced were that the positive stimulus could not occupy the same position twice in succession, and that all 6 locations had to be tested 5 times in each daily session of 30 trials. The animals received 10 daily sessions.

TABLE 9 FOOD BOARD RESULTS NO. OF ERRORS

Set A	*Board I* (*10 trials*)	*Board II* (*10 trials*)		*Total*
Parietal				
94	3	1		4
92	3	0		3
96	3	6		9
101	0	1		1
			Mean =	4.25
Prestriate				
102	9	16		25
89	27	16		43
90	4	16		20
			Mean =	29.33
IT				
93	36	39		75
95	62	36		98
91	12	19		31
97	130	25		155
			Mean =	89 50
Set B	*Board II* (*10 trials*)	*Board I* (*10 trials*)		
Unoperated				
205	0	0		0
210	2	0		2
203	5	2		7
			Mean =	3.00
Fundus				
204	3	2		5
209	8	0		8
200	8	0		8
			Mean =	7.00
Prestriate				
201	14	5		19
219	3	2		5
191	3	2		5
			Mean =	9.67
AIT				
195	10	4		14
192	28	14		42
188	12	2		14
			Mean =	23.33

Set B animals went through a similar experiment, except that the positive stimulus ('3 cylinders', *see* fig. 3 and Appendix) would have slightly different retinal configurations at different locations in the testing board. The Method was otherwise identical to that used above.

Results

Food board analysis. Analysis of the data revealed no strong or consistent bias towards any position, except that the IT and prestriate groups tended to make slightly more errors in the central loci on the board, that is, when they were surrounded by the greatest number of other stimuli.

Six-choice transform analysis. The data for all six-choice problems combined are shown in Table 10. The errors are classified according to whether they occurred with the positive object in the central 2 positions, the positions one step or two steps away from the central positions. Both transform and nontransform errors were somewhat more likely to occur at the extreme end positions (± 2) than at other locations.

TABLE 10. NO. OF ERRORS AT DIFFERENT POSITIONS OF POSITIVE OBJECT

	Nontransforms			*Transforms*		
	Centre	*± 1*	*± 2*	*Centre*	*± 1*	*± 2*
Parietal	0	2	4	8	11	13
Unoperated	4	9	9	19	16	34
Fundus	0	0	5	19	16	25
IT	10	4	16	40	42	33
Prestriates, Sets A+B	14	21	32	62	73	98
AIT	16	10	21	50	41	59

Two objects in six positions. The results of the two tests are shown in Table 11. With the 'Reel' problem there was only a slight tendency for the IT and prestriate groups to be worse than the parietal (5.0% and 2.67% errors, respectively, compared with 1%). With the '3-cylinder' problem, all groups are at ceiling except the AIT animals, 2 of whom tended to make more errors at extreme loci. These findings, taken together with those above, might be taken to indicate that position *per se* does not introduce a difficulty for the IT animals when the stimuli are well learned (as with food objects) or do not change their retinal configuration as a function of position (the reel). With the more difficult 3-cylinder problem, perhaps movement to an extreme position is equivalent to a minor orientation transform, which might in itself make the task somewhat more difficult for the inferotemporal animals.

TABLE 11. TWO-OBJECT SIX-POSITION TEST NO OF ERRORS

	Position						
	1	*2*	*3*	*4*	*5*	*6*	*Total*
Reel							
Parietal	1	0	0	0	0	2	3
Prestriate	3	2	2	0	0	1	8
IT	3	2	4	1	2	3	15
Total	7	4	6	1	2	6	26

	Position						
	1	*2*	*3*	*4*	*5*	*6*	*Total*
3 Cylinders							
Unoperated	0	0	0	0	0	0	0
Fundus	1	0	0	0	0	2	3
Prestriate	1	0	0	0	0	0	1
AIT	17	2	1	1	5	12	38
Total	19	2	1	1	5	14	42

V. PERFORMANCE AS A FUNCTION OF OBJECT DISCRIMINABILITY: CONE PROBLEM

It could be argued that the transform problems might have been inherently more difficult than the nontransform problems, for two reasons: first, that they were novel and less well practised; secondly, that in the two-choice situation the transform and negative objects were deliberately made to be similar to each other in orientation and size, whereas nontransform objects were merely randomly paired with a single negative object to which no such constraints applied. And, even though in the six-choice situation no effort was made to match any of the negatives with the transform object, the probability of at least one of the novel negatives being similar to the positive object was higher than in the two-choice situation. It was considered useful, therefore, to examine difficulty of object discrimination *per se*, relatively unconfounded either by degree of experience with any particular object or by the use of transforms as such. The object discrimination set consisted of solid cones of constant volume but of different solid angles of their apices. Such stimuli have the double advantage of being capable of being varied along a single dimension of difficulty and also of producing an invariant retinal configuration at all positions on the testing board.

Methods

As a preliminary stage of learning, all animals in Set A were trained on a discrimination between a very wide cone (No. 6, 134.4 deg) as the negative stimulus and a much narrower one (+, 74.4 deg) as the positive. The animals were trained on this task, as a two-choice problem until they reached a criterion of 90 per cent correct in 100 successive trials. As the + cone had just been used as the positive object in the immediately preceding six-choice problem, this preliminary stage constituted, in effect, a confirmation of retention of this object as positive. In fact, all animals in all groups reached criterion without error.

They then proceeded to the formal experiment in which they were presented with the + cone *vs* each of cones No. 1 to No. 5 in random order (except that the same negative cone was not allowed to occur twice running). The angles of the cones + to 6 varied in steps of 10 deg. Each animal received 30 trials per day, 6 each of cones 1, 2, 3, 4 and 5. Correction trials were not given. All animals received 1000 trials, 200 of each of the 5 cones *vs* the + cone.

At the next stage, because improved levels of performance approached ceiling, the difficulty was further increased by introducing a new cone with an angle half-way between that of the + stimulus and No. 1 cone, that is, a difference in apical angle of 5 deg, which was designated as cone No. ½. Cone No. 5 was dropped from the series, and the animals were given a further 1000 trials, 200 each of cones ½, 1, 2, 3 and 4.

In order to reduce the possibility of artefacts, several versions of the + cone were made and all cones were repainted frequently. The plastic plaques on which they were mounted were also changed daily.

Results

The basic data consist of the percentage correct performance for each cone *vs* the + stimulus, as a function of the time in the experiment. A useful further way of summarizing the data is to calculate, by interpolation, the threshold value of apical angle that an animal can just discriminate. This can be defined arbitrarily as the value of cone which produces 75 per cent correct performance. Table 12 summarizes the percentage correct performance for each animal at both phases of the experiment, and fig. 8 shows the 75 per cent threshold values plotted against blocks of 200 trials of training.

TABLE 12 CONE SERIES

	Phase 1, cones 1–5							*Phase 2, cones ½–4*					
	No of errors made in 200 trials of each cone no.					*Total errors*		*No of errors made in 200 trials of each cone no.*					*Total errors*
	1	*2*	*3*	*4*	*5*			*½*	*1*	*2*	*3*	*4*	
Parietal													
94	26	10	1	0	0	37	94	52	0	0	0	0	52
92	43	10	1	0	0	54	92	76	18	2	0	0	96
96	31	19	3	0	0	53	96	82	21	2	0	0	105
101	33	14	1	0	0	48	101	75	13	1	0	0	89
Prestriate													
102	66	30	12	0	0	108	102	61	22	14	1	0	98
90	56	45	9	0	0	110	90	78	37	13	2	0	130
89	87	81	55	18	0	241	89	97	64	45	24	6	236
IT													
93	41	21	4	0	0	66	93	73	6	1	0	0	80
95	85	61	35	9	3	193	95	99	49	20	8	1	177
91	91	70	54	20	10	245	91	87	56	34	12	2	191

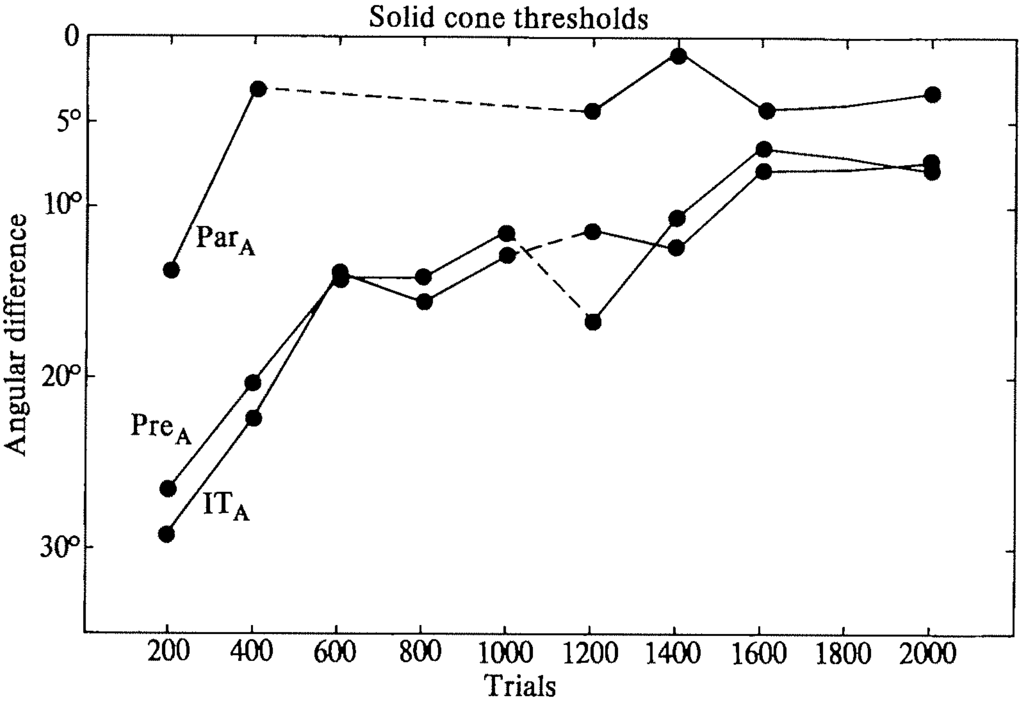


FIG 8 Mean thresholds for cone discrimination as a function of trials of practice. Abbreviations as in text.

It will be seen that group data show a difference between the prestriate and IT temporal groups, on the one hand, and the parietal group on the other. As training proceeded performance tended to improve and the difference between groups was diminished. Therefore those groups that were impaired on object learning and object transforms were also less sensitive in cone discrimination, at least over several hundred trials, although in terms of ultimate capacity all three groups appear to approach the same asymptote.

The important question is whether an animal who is poor on learning and on transforms is necessarily insensitive in cone discrimination. Although it is reasonable to assume that the opposite is likely to be true, evidence against such a view is the fact that monkeys with lateral striate lesions have poorer angle discrimination thresholds than monkeys with posterior inferotemporal lesions, while the latter are poorer at learning pattern discriminations (*see* Blake *et al.*, 1977). In examining individual data, one IT animal (No. 93) was consistently poor in initial learning and in identification of transforms, but was well within the scores of the parietal controls in terms of cone sensitivity. This was true from the very start of the experiment. In the first 200 trials, his 75 per cent threshold was a cone value of 19 deg, compared with values for the 4 parietal animals of 16, 16 and 23 deg, and one with a value of less than 10 deg (i.e., not measurable at that stage). Values comparable to the control group continued to be produced consistently by this animal throughout the entire experiment. In terms of response to transforms in the previous experiments, on the other hand, this animal fell squarely in the range of the IT group, and well outside that of the parietal group. One animal in the prestriate group also, No. 90, who was notably poor on transforms (although not on initial learning), rapidly improved his cone sensitivity performance, so that after 400 trials he was well within the parietal range, and his threshold was less than 10 deg and remained at that level thereafter. (During the block of 400–600 trials his performance on the most difficult cone discrimination, 10 deg, was 80 per cent, compared with a mean of 83 per cent for the parietal group.) Therefore it seems that the transform deficit is not dependent necessarily on a lack of sensitivity of discriminability *per se* even at the outset. There is evidence to show that the ultimate sensory capacity of IT animals is normal (Ettlinger, 1959; Symmes, 1965; Cowey and Weiskrantz, 1967; A. Cowey, P. Dean and L. Weiskrantz, unpublished (normal contrast sensitivity functions in AIT monkeys)), and here also the asymptotic values of all groups appeared very close. The interpretation of these, and other test results, will be considered further in the Discussion.

It might be noted that one animal in the prestriate group, No. 89, appeared to be disproportionately poor at cone discrimination compared to the other 2 animals in that group, and throughout the whole experiment remained the worst animal amongst all groups. Therefore his difficulty with transforms might have been affected by a sensory problem, although there was nothing in the histology (*see above*) to support this supposition. As already noted, his lesion was not dissimilar to the others in the prestriate group.

DISCUSSION

The main points in the results can be summarized as follows. The animals with inferotemporal or prestriate lesions were impaired in identifying the transforms of objects after having learned the objects in their original untransformed mode. In relation to the other groups, the IT animals, especially the AIT monkeys, had difficulty in the initial learning or relearning of objects or two-dimensional pattern discriminations. They also had an impairment on food board testing. The prestriate groups had a partial deficit on these tasks. Both of these groups also had an impairment in threshold for conical solid angle discriminations, although with practice they closely approached the sensitivity of control groups. There was no effect of lesions of the fundus of the superior temporal sulcus or the posterior parietal lobe.

As regards the importance of the limits of the lesions, overall the results broadly favour increasingly severe discrimination learning, food board, and pre-post savings deficits the further forward the lesion extends in the inferotemporal region. For a prestriate lesion, the more it extends ventrally into the posterior inferotemporal region, the more severe the transform deficit.

What are the implications of this pattern of findings for inferences about the organization of the visual system and mechanisms of object recognition? The results are consistent with the view that the more anterior portions of the temporal lobe tend to be critical for storing a 'prototype' of a visual object, and to store it in a form that is accessible to and independent of (within limits) various transforms. A lesion produces a severe deficit in acquiring this stored knowledge (and abolishes the recognition of previously acquired discriminations; *see* Dean and Weiskrantz, 1974), and we also make the assumption that when it is acquired, albeit slowly, its stored specification is less precise and less complete than in control animals. The evolutionary advantages for storing knowledge about specific shapes and objects in the form of prototypes are very great, otherwise each specific variation of a shape would have to undergo separate association with other events that attach relevant meaning to it. The statistical impossibility of such an alternative arrangement is of the same order as that which makes a statistical basis for sentence recognition an impossibility (Chomsky, 1968). An adequate prototype would be a prerequisite both for further associations being formed between the object and meaningful rewards and punishments—and hence the recognition of food *qua* food is impaired—and also for being 'addressed' by various transforms of the object—and hence the transform deficit.

We assume, further, that the posterior regions of the inferotemporal cortex are more concerned with the processing involved in the addressing of transforms, and less concerned with storage of the prototype as such. Therefore there is a transform deficit, but having a different origin than the inferotemporal deficit. In animals with prestriate lesions, we assume, prototypes can be formed if the animals are not required to cope with transforms during the learning phase. Moreover, if transforms do not intrude after that stage, then 'meaning' can be attached and be maintained relatively normally, as reflected in the food board results for the animals with prestriate lesions. But, having learned a problem in which the stimuli have been nontransformed (and at a more efficient rate than the anterior groups do), their difficulty with transforms is revealed during the specific probe trials when transforms are first encountered.

It has already been demonstrated that the poor performance of experimental groups on transforms cannot be accounted for by a nonspecific performance impairment on both transforms and nontransforms. But another possible explanation of the findings might be that the prestriate and IT animals' deficit simply reflects task difficulty: the transforms are novel stimuli to be learned in the same way as any other discriminanda, and it is known that these groups have a learning deficit. There are serious difficulties with such an argument, however. First, the AIT animals clearly have much more difficulty in learning new object discriminations, and yet their transform impairment is no more severe than that of the prestriate group. Secondly, as has already been seen, the difference between groups emerges on the first transform trials, that is, before the opportunity for new learning of transforms becomes an issue. Thirdly, an inspection of single cases reveals highly striking dissociations between learning and transform performance. Consider prestriate Monkey 201 (in Set B). It happens that he learned the 'hexagonal nut' problem in zero trials; that is, he reached 90 correct out of 100 trials with no further training, and so had considerable overtraining on the standard object which he found very easy. Yet he made 22 errors on transform trials (i.e., 36.7%) (of these, 5 were on shadows, 12 on orientation, and 5 on size). And yet on the baseline nontransform trials in which the transforms were embedded, he made only 3 errors (i.e., 1.25%). It happens that this problem was also a relatively difficult one for the unoperated group on transforms, but none showed such poor performance or degree of dissociation. An even more striking example, perhaps, is the 'T-piece' problem for Set A animals. All of the animals found the task extremely easy—every animal in every group made criterion in zero trials (perhaps because it was somewhat similar to the immediately preceding problem). Yet the 3 prestriate animals made 23.3, 23.3 and 28.3 per cent errors, respectively, on transform trials, compared with a range of 0 to 6.7 per cent for the parietal animals, nor was there any overlap between the parietal and IT groups. (The errors of the prestriate group were, again, distributed among all types of transforms: 12 on shadow, 25 on orientation, and 8 on size.) Within operated groups striking contrasts can be found. For example, Monkey 192 in the AIT group found the 'T-piece' problem relatively easy—41 trials to criterion. Monkey 195 in the same group found it very difficult—637 trials. Yet the two animals made about the same number of errors on transforms (25.0% and 26.7%).

It is difficult to see how a sensory capacity loss could account for a difficulty with transforms as such, at least in the six-choice paradigm. It would be necessary to argue that the transformed object was somehow more likely than the nontransformed to be paired with a closely similar stimulus object, and in the design of the experiment this can be excluded. But the present scheme must deal with the results of the conic solid angle experiments. The question is why the prestriate and IT groups had impairments when they were first given the cone discrimination series, and required training to overcome it. Considering the IT group, there is no difficulty in explaining the results on the assumption that their prototype is less sharply defined. This is equivalent to saying that they should demonstrate greater discrimination generalization along a single dimension, and there is supportive evidence for this (Howlett, *see* Weiskrantz, 1974; Dean, 1976), and also should demonstrate greater interference among different visual objects in discrimination learning and retention (Weiskrantz, 1967; Iwai and Mishkin, 1968; Cowey and Gross, 1970; Iversen, 1970). There is also evidence that monkeys with IT lesions acquire less complete information than controls about visual discriminanda (Butter and Gekoski, 1966; Iversen and Weiskrantz, 1967).

The results for the prestriate group are less easy to understand, because the cone discrimination was chosen to minimize the problem of retinal transforms caused by a change in position of the stimuli in the testing chamber. The sensory capacities of the prestriate monkeys have still not received much research. The present results agree with the findings of Blake *et al.* (1977) in which animals with either posterior or anterior IT lesions had a slightly reduced threshold for two-dimensional angle discrimination (although the threshold values in that study are paradoxically quite high). There is also a suggestion of a slight reduction in acuity in monkeys with prestriate lesions as measured by the high spatial frequency cut-off point in the contrast sensitivity function (A. Cowey, P. Dean and L. Weiskrantz, unpublished), but the effect is weak (and nonexistent for AIT lesions). Wilson and Mishkin (1959) also found a slight elevation in threshold for size discrimination for two-dimensional stimuli. The foveal prestriate group, therefore, may have a slight sensory loss of minimal separable acuity, not in itself an unreasonable expectation given that this region receives a direct input from the foveal area of striate cortex, and this may be an adequate explanation of why these animals had greater difficulty with the cone problem than did the controls. We have also seen that the analysis of results of individual animals showed that the transform deficit did not have a tight relationship with cone threshold performance, and that it is possible that the two are independent and dissociable.

A paradox still remains for the prestriate animals. As the hypothesis has been stated so far, whether or not they had a slight sensory loss, they might have been expected to show a more rapid improvement in their threshold values with training than the inferotemporal animals. The hypothesis therefore needs to be considered somewhat more explicitly.

When any particular example of an object is viewed, in order for it to be classified in terms of a particular prototype it must be given a set of descriptors or specifications relevant to object shape. How the nervous system actually performs this process is unknown, but various approaches have been outlined, such as Marr (1982) who discusses the stages of processing between the initial image, the 'primal sketch' which makes explicit various aspects of geometrical distribution of intensity changes, to a more explicit representation of orientation and approximate depth of surfaces and contours, but *in a viewer-centred* coordinate framework, and finally to the stage of a three-dimensional representation of a shape in an *object-centred* canonical coordinate system. There is a progression, that is, from a retinotopic framework at the stage of output from striate cortex to an 'objectotopic' framework when prototypical representation has been achieved. We assume that the prestriate lesion causes an impairment in the accuracy with which such a set of descriptors, probably still in a viewer-centred framework, is prepared for transmission to the locus of the stored prototype itself. The descriptors for a set of cones with slightly varying apical angles would be highly similar. With inaccurate descriptor information, various cones are likely to be confused with each other, or more precisely all to be addressed to a single prototype rather than to the relevant dimension of angular separation, so that the prestriate group will be impaired in their discriminations of closely similar objects.

The relevant relationships are outlined in fig. 9. A functional separation between anterior and posterior inferotemporal regions is supported by lesion evidence (Iwai and Mishkin, 1968; Cowey and Gross, 1970) and also by the report that neurons in

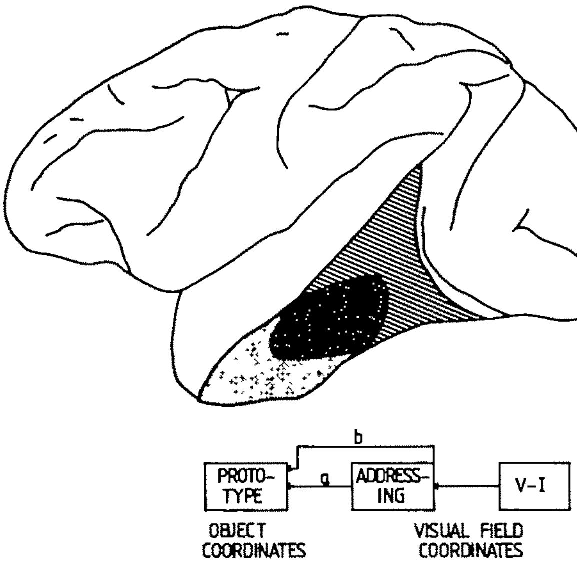


FIG. 9. Hypothetical schema for stages of visual processing in striate (V-I), posterior and anterior inferotemporal cortical regions. Sets of varying outputs from the visual projection area resulting from transformed views of objects are addressed *via* route (a) to the prototype store. Route (b) is included to admit the possibility of a direct route to the prototype store for invariant views of objects such as spheres, or for dimensions such as brightness or colour.

the anterior portion of the inferotemporal cortex have larger receptive fields (Desimone and Gross, 1979). Two qualifications need to be introduced. First, it is assumed that the inferotemporal cortex is, in reality, not sharply divided geographically into separate loci for processing, but that rather there is a gradient from posterior to anterior corresponding with an increasing concern with prototype storage and a decreasing concern with descriptor construction. The dissociations between the effects of anterior *vs* posterior inferotemporal lesions (Iwai and Mishkin, 1968; Cowey and Gross, 1970) on concurrent learning *vs* pattern learning are consistent both with the argument advanced above for different stages of processing between the two regions and with the assertion that there is an anatomical overlap. Secondly, the lesions that are made in actual practice themselves have some overlap, and of course the inferotemporal lesions of Set A overlap with both the anterior inferotemporal and prestriate lesions of Set B. Therefore the lack of differentiation between prestriate and the two IT groups on the transform trials is not unexpected. Even without any overlap of lesions or of processing within the temporal lobe, theoretically one would expect single and not double dissociation between the anterior and posterior regions, such that the anterior group showed impaired learning, and both the anterior and posterior groups showed impaired transform performance. That is, we assume that the relationship between descriptor construction and the prototype store is serial and hierarchical.

The fact that the IT and prestriate animals tended to be poorer at cone discrimination carries the implication that their difficulty with transforms cannot be due, as such, to an impairment in judging the similarity between objects. On the contrary, they appear to be more likely to treat similar objects as identical. Equally, the generalization data of C. Howlett (unpublished results, *see* Weiskrantz, 1974) show that monkeys with inferotemporal lesions have flatter gradients than control animals, that is, they treat a wider family of lines of increasing tilt as equivalent to each other than do the controls. But even (to us) relatively minor changes in size or shadows lead to a greater probability of judgements of nonidentity in the temporal lobe groups. Indeed, it is even possible that the performance of these groups might have been worse but for their enhanced tendency to treat closely similar stimuli as equivalent, because the transformed objects must have had some dimensional similarity to the nontransformed objects. For example, a change in size would not disturb the tilt or angularity of any of the edges of the objects. Judgements of object identity in the face of retinal transformations appear to involve a different level of processing from that involved in sharpness of discrimination along a single dimension, and it is difficult to relate success in dealing with object transforms in terms of generalization gradients along single dimensions.

The fundus and parietal lobe lesions were without effect: the parietal group, as mentioned above, may even have been superior to an unoperated group; if so, it seems likely that this is because of a decreased dependence on spatial over shape factors in their discriminations. The fundus lesion was included because of the evidence from Jones and Powell (1970) that area TE of inferotemporal cortex sends a projection to that region, and in a hierarchical progression it seemed a possible candidate for the next stage of processing towards higher degrees of abstraction beyond the inferotemporal region. Clearly the limited region of fundus of the superior temporal sulcus lesioned in this study does not play a critical role, but it may be that the lesion would have to extend much further anteriorly before the question of its importance for object learning or transform discrimination can be finally settled. It appears, for example, that 'face neurons' can be recorded from the anterior two-thirds of the fundus (E. T. Rolls, personal communication).

There appear to be very few animal studies in the literature that have dealt with the specific questions addressed here. Yaginuma *et al.* (1982) reported that monkeys with inferotemporal lesions had difficulty in discriminating visual patterns when they were reduced in size, a result that is puzzling given the normal acuity of such animals. But they also mention unpublished results of Osawa and Iwai that there was no deficit 'provided that both the patterns *and* the background plaques were proportionally reduced'. In other words, the reduction in size of the pattern alone was equivalent to a size transform, as the term is used in the present study. It is because of their findings that we have analysed the performance both with large and with small transforms separately. Although the small transform was somewhat more difficult than the large, nevertheless our experimental groups were impaired on *both* transforms. Interestingly, Yaginuma *et al.* also refer to another study of

Iwai *et al.* (1976) about which it is said that after monkeys with inferotemporal lesions had learned pattern discrimination 'they failed to perform the discrimination when the outline triangle (the positive stimulus) was simply rotated clockwise or counterclockwise by 120 degrees' (p. 30). Our findings are also quite consistent with the interesting paradoxical results of Gross (1978), and his interpretation of them, in which he found that monkeys with inferotemporal lesions were *not* impaired in learning to discriminate between mirror symmetric visual patterns, but were impaired, as usual, in discriminating between asymmetrical ones. He suggests that perhaps the normal monkeys viewed the rotated patterns as identical, whereas the experimental animals did not, which would make the task relatively more difficult for the controls.

Studies of 'perceptual constancy' are obviously relevant, and the evidence of Humphrey and Weiskrantz (1969) that monkeys with inferotemporal lesions (also invading portions of prestriate cortex) are deficient in size constancy supports the present position. The impaired animals tended to alternate between retinal image and distance as strategies rather than integrating the two (but it is important to stress that such animals show no evidence of distorted or unstable vision; they appear normal in their everyday visual behaviour). Ungerleider *et al.* (1977) replicated the finding that inferotemporal lesions produced a size constancy impairment, and showed also that prestriate lesions caused a size constancy impairment such that the animals depended mainly on retinal image size rather than distance. This suggests that the use of distance information is critically dependent on prestriate cortex or structures earlier in the anatomical sequence. Both studies can be interpreted as showing that animals with inferotemporal lesions, especially when posteriorly placed, are reduced to a greater dependence upon 'viewer-centred' coordinates (retinal size or apparent distance from the observer) rather than on 'object-centred' coordinates (which are a joint multiplicative function both of retinal size and distance, *see* Humphrey and Weiskrantz, 1969).

Gross and Mishkin (1977) have argued that, because of the very large size of receptive fields of inferotemporal neurons, lesions in this area may produce a deficit in retinal generalization, that is, in recognizing the identity of a shape independently of its position in the visual field (within the limits imposed, of course, by acuity and optics). There is no evidence from any direct tests of that suggestion, although the evidence from Gross and Mishkin that inferotemporal lesions plus optic chiasm section cause an impairment in interocular transfer (i.e., produce, in effect, a split-brain preparation) is consistent with it. Here we would broaden the argument considerably, because it is reasonable to presume that the animals in the present study viewed the objects with the central part of their fields, and that no serious problem of retinal generalization intruded. For example, the temporal lobe animals were impaired by a change in the pattern of shadows after having learned the nontransform version of the object. We would argue that lesions of the temporal lobe of monkeys will disturb any performance that requires a representation of a visual shape in terms of an 'object-centred coordinate system' or 'prototype' to be constructed or addressed by information from an earlier stage of processing based on changing retinal information from a 'viewer-centred coordinate system'.

The evidence from this study has its obvious links with clinical evidence that posterior right hemisphere lesions cause a difficulty in the identification of 'unusual views', even though identification of the prototype is preserved (Warrington and Taylor, 1978). A similar approach to visual agnosia in terms of Marr's theoretical speculations has been discussed by Ratcliff and Newcombe (1982). No precise definition of the configurational properties of the prototype itself emerges from either source, although in man it is assumed to be a stereotypically portrayed view of an object. Here the definition is entirely operational, based on what the animal was first given to learn as the positive (and hence meaningful) stimulus, although it is assumed, of course, that the representation of the object will not be restricted to the literal form used in training but will be orientation-free and coded in terms of the most economical canonical axes.

In the human case it is not possible to separate the acquisition and maintenance stages of prototype formation from the identification stage involving transforms, and even in the animal evidence one is concerned with a gradient rather than a sharp dissociation within a region in which both anterior and posterior lesions produce a transform deficit (although hypothetically for different reasons). The present results agree with those of Warrington and her colleagues (Warrington, 1982) that changes in orientation *or* shadow arrangement will reveal the deficit (also, *see* Benton and Van Allen, 1968, for the effect on patients of such transforms of pictures of faces). In addition, the monkey deficit, unlike the human one, is apparently sensitive to changes in size, but there are many procedural differences that might account for this difference. In any event, it is not sufficient to interpret the results of either the human or animal studies as reflecting only a particular difficulty with foreshortening of canonical axes, as has been implied (Marr, 1982). In man (Warrington, 1982) there is specialization of the right hemisphere for the 'unusual views' impairment—indeed, an argument can be made on grounds of economy that specialization should have been achieved at or by the stage at which the representation of the prototype has been specified (Weiskrantz, 1979)—and the further stage of attachment of functional meaning is presumed to occur in or depend critically upon the left hemisphere, as displayed in cases of associative visual agnosia. In the present experiments the lesions were bilateral and it cannot be said whether the combined anterior inferotemporal regions are equivalent to the left hemisphere stage of processing in man, or whether in the monkey, too, there might also be hemispheric specialization, as there appears to be from preliminary evidence (Jason *et al.*, 1984) for visuospatial capacity.

ACKNOWLEDGEMENTS

We are pleased to express our appreciation for assistance at various stages of the experiments to Mrs Anna Thornton, Mr Martin Holland, Dr Richard Platt and Dr Paul Dean. We are grateful to Dr Nick Rawlins for help with the statistical analysis.

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(*Received December 6, 1983. Revised April 12, 1984*)

APPENDIX

DIMENSIONS OF STIMULUS OBJECTS

(Problems numbered in order of presentation)

Set A

Two-choice

Problem 1. '3 cylinders'. Colour. blue. *Nontransform*: 3 cm high; each cylinder 0.8 cm in diameter. *Large size transform*. 4 cm high, 1.30 cm in diameter. *Small size transform*: 2 cm high, 0 6 cm in diameter.

Problem 2. 'Elbow'. Colour: orange. *Nontransform*: length of outer surface 8.8 cm; diameter 2.5 cm. *Large size transform*: length of outer surface 10.2 cm; diameter 3 cm; *Small size transform*: length of outer surface 5.8 cm; diameter 1.5 cm.

Problem 3. 'T-piece'. Colour: orange. *Nontransform*: 5.6 × 2.5 cm outer dimensions, diameter 2.5 cm. *Large size transform*. 6 5 × 5.5 outer dimensions, diameter 3.0 cm. *Small size transform*: 4 4 × 3.7 cm, diameter 1.6 cm.

Problem 4. 'Bowl'. Colour: green. *Nontransform*: diameter 3.2 cm, height 1.4 cm. *Large size transform*: 4.2 cm diameter, 2.4 cm height. *Small size transform*. 2.2 cm diameter, 0.7 cm height.

Six-choice

Problem 5. 'Cone'. Colour: green. *Nontransform*: height, 2.5 cm, diameter of base 3.8 cm, apical angle 74.4 deg. *Large size transform*: height 4.0 cm, diameter of base 4.0 cm, angle 74.4 deg. *Small size transform*: height 2.0 cm, diameter of base 2.8 cm, angle 74.4 deg.

Problem 6. 'Half-ball'. Colour: green. *Nontransform*: diameter 3.8 cm; height 2.0 cm. *Large size transform*. diameter 5 3 cm; height 2.9 cm. *Small size transform*: diameter 2.7 cm; height 1.0 cm.

Set B

Two-choice

Problem 1. '3 cylinders'. Same as Problem 1 above.

Problem 3. 'T-piece'. Same as Problem 3 above.

Problem 5. 'Hexagonal nut'. Colour: red. *Nontransform*: length of each hexagonal edge 2.1 cm; diameter of inner hole 2 1 cm; thickness 2.1 cm. *Large size transform*. length of each edge 2 8 cm; diameter of hole 2.8 cm; thickness 2.8 cm. *Small size transform* length of each edge 1.4 cm, diameter of hole 1.4 cm; thickness 1.4 cm.

Six-choice

Problem 2 'Cone'. Same as Problem 4 above.

Problem 4. 'Reel'. Colour: green. *Nontransform* outer diameter 3.8 cm; height 3 0 cm; each indentation 2 6 cm in diameter, height 0 6. *Large size transform*: outer diameter 4.8 cm; height 4.5 cm; indentation 3.0 cm in diameter, height 0.9 cm. *Small size transform*: outer diameter 2 8 cm; height 2.0 cm; indentation 2.0 cm in diameter, height 0.4 cm.

Problem 6. 'Star'. Colour: yellow *Nontransform*: overall diameter 4.5 cm; diameter of each spoke 0.5 cm, diameter of inner hub, 1.5 cm. *Large size transform*: overall diameter 6 0 cm; spoke diameter 0.75 cm; diameter of hub, 2.0 cm *Small size transform*: overall diameter 3.0 cm; spoke diameter 0.25 cm; diameter of hub 0 25 cm.

Brain (1984), **107**, 1073-1082

CONGENITAL TRIGEMINAL ANAESTHESIA

A REVIEW AND CLASSIFICATION

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SUMMARY

Forty-three patients with the syndrome of congenital trigeminal anaesthesia (CTA) have been reported to date. The cases have been divided into three groups based on the presence and nature of any associated clinical problems. Three additional cases are presented as characteristic of each of the groups. A different aetiology is proposed for each group.

Group I consists of patients with CTA as an isolated finding. It is almost always bilateral, and typically involves the distribution of only the first division of the fifth nerve. There is no evidence of other neurological abnormalities or associated mesoectodermal congenital anomalies. The aetiology is suspected to be a primary neural hypoplasia.

Patients with associated congenital mesenchymal anomalies were placed in the second group. CTA was often a minor part of another well defined, more extensive clinical syndrome, such as Möbius or oculoauriculovertebral dysplasia (OAVD). The sensory abnormality was either unilateral or bilateral. The skin of the face was almost always involved, as well as the cornea and conjunctiva. This may be a heterogenous group with multiple aetiologies having in common an injury early in embryogenesis.

The third group is defined as patients with CTA without evidence of mesenchymal dysplasia. These cases differ from the first group primarily because of the presence of associated focal brainstem signs. The aetiology is thought to be due to focal neural dysgenesis secondary to a prenatal injury, possibly vascular in nature.

INTRODUCTION

Congenital trigeminal anaesthesia (CTA) is a rare clinical finding that may be seen in a variety of clinical settings. It can be defined as a stable congenital deficit involving all or part of the sensory function of the fifth cranial nerve. The only review of this topic was undertaken by Hewson (1963). He found 14 cases reported in the literature, and proposed that the aetiology in all cases was a 'developmental anomaly of the brainstem'. He made no attempt at a classification of the cases.

To date 43 cases have been reported in the literature. A review of these cases suggests that they can be divided into three groups based on the presence and type of any associated abnormalities. Three additional cases are reported emphasizing the clinical differences and characteristics of each group.

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In the first group are patients with isolated CTA. Their deficit is typically bilateral and limited either to the cornea and conjunctiva, or to the distribution of the first division of trigeminal nerves. Only one case has been reported with associated involvement of the second division. There is no evidence of other cranial nerve dysfunction or mesenchymal tissue abnormalities.

The second and largest group consists of patients who had CTA associated with multiple developmental anomalies. There is a frequent involvement of tissues of both ectodermal and mesodermal origin such as muscle, bone and hair, with or without additional malfunction of the nervous system.

The third group is made up of patients with CTA whose associated neurological features indicate focal intrinsic brainstem dysfunction. They have no evidence of associated somatic structural abnormalities.

CASE REPORTS AND LITERATURE REVIEW

Case 1

The patient, a male aged 4 years, suffered from recurrent corneal ulceration bilaterally that began at the age of 12 weeks. The absence of corneal sensation was not noted, however, until the age of 2 years. At 4 years of age the examination was remarkable for multiple scars about the forehead and bilateral corneal ulceration. He had an alternating esotropia, but no dysmorphic features or developmental anomalies. Neurological examination was normal except for absent corneal reflexes bilaterally and a consistent indifference to pin prick in the distribution of the first division of the fifth nerve, also bilaterally.

X-rays of the skull and skeletal system were normal. The EEG and auditory evoked responses were unremarkable. Cranial CT scans with horizontal and coronal cuts revealed mild hypoplasia of the cerebellar hemispheres as well as the brainstem (fig. 1). Additionally there were enlarged lateral ventricles without evidence of cortical atrophy.

The patient has been treated with multiple tarsorrhaphies and patching, but continues to suffer from recurrent ulcers. The interval, however, between these episodes has been increasing with age.

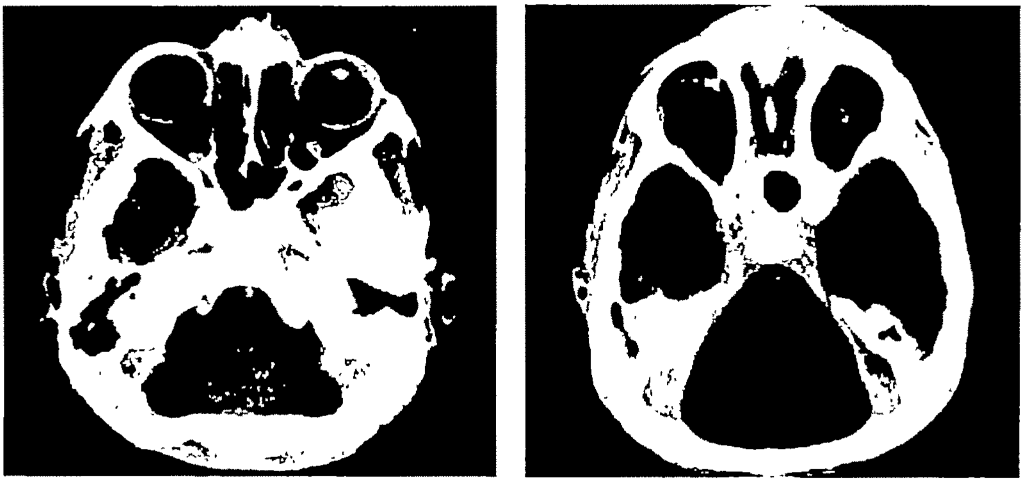

FIG. 1. *Case 1.* CT scans showing brainstem and cerebellar hypoplasia.

Comment

CTA as an isolated finding has been reported in 23 patients (Group I). Thirteen of these were members of a single family reported by Purcell and Krachmer (1979), and will be discussed separately. The 10 sporadic cases (Table 1) had a striking tendency to be bilateral, only one being unilateral. The conjunctiva and cornea were anaesthetic in all cases, and were the only areas affected in 4 (40%). In these cases the condition has been referred to as congenital corneal anaesthesia (Anseth, 1968). When the skin of the face was also involved, the first division of the trigeminal nerve was the sole branch affected in all but one patient. That child had anaesthesia of the first and second divisions bilaterally (Van Milligan, quoted by Bernd, 1930).

All presented with corneal ulceration before the age of 3 years, usually between 8 and 12 months. Although some had bilateral ulceration when first seen, the majority presented with only one eye affected. Ulceration of the second eye typically developed within a year, but in one patient it occurred as late as seven years subsequently (Bernd, 1930). In another case the opposite cornea, although anaesthetic, had not yet become ulcerated with follow-up to the age of 7 years (Anseth, 1968).

Purcell and Krachmer (1979) reported a family with 13 of 25 family members over 4 generations who showed a decrease in corneal sensation as an isolated defect. The pattern of inheritance was not mentioned. Six had defects bilaterally and 7 only

TABLE 1 CLINICAL DATA FOR GROUP I CASES

Author, sex/age (yr published)	*Ocular sensation*	*Facial sensation*	*Corneal ulceration (age first noted)*
1. Lawford F/6 (1907)	Decreased RE Absent LE	Normal	LE (2 yrs)
2. Kayser M/4 (1921)	Absent bilat.	V1 bilat. decreased	Bilat. (1 mo)
3. Bernd F/9 mo (1930)	Absent bilat.	V1 bilat. decreased	LE (9 mo) RE (8 yrs)
4. Van Milligan F/? (quoted by Bernd)	Absent bilat.	V1, V2 absent	Bilat. (NM)
5. Hewson F/2 (1963)	Absent bilat.	V1 bilat. decreased	RE (1 yr) LE (17 mo)
6. Leydhecker M/3 (1964)	Absent bilat.	Normal	LE (3 yrs) RE (4 yrs)
7. Anseth F/7 (1968)	Absent bilat.	Normal	RE (23 mo)
8. Stewart *et al.* F/11 mo (1972)	Absent LE	L V1 absent	LE (11 mo)
9. Carpel M/6 (1978)	Absent RE, Decreased LE	Normal	Bilat. (NM)
10. Rosenberg M/4 (1984)	Absent bilat.	V1 bilat. decreased	Bilat. (3 mo)

LE = left eye, RE = right eye, NM = not mentioned.

unilateral hypaesthesia. Although there was no gross ulceration in any patient, slit lamp examination revealed that 3 had diffuse punctate erosions of the cornea. Each of these responded promptly to patching.

Case 2

The patient, a female aged 4 years, was born at seven months gestation without other complications. Shortly after birth she was noted to have multiple abnormalities, including an occipital meningoencephalocoele, hypoplastic pinnae, a complete right and a partial left facial paralysis, and poor motion of the left vocal cord. Surgical correction of the skull defect was not performed. She developed a corneal ulcer in the right eye at the age of 5 months, and decreased sensation of the right cornea was first noted at that time. She was treated successfully with patching and as a result ulceration has not recurred.

Examination at 3 years of age showed a 0.5 cm occipital skull defect. The ears were low set and slightly deformed, but there were no preauricular nodules. The pectoral muscles were mildly hypoplastic bilaterally. Neurological examination revealed a marked developmental delay. Extraocular movements showed a bilateral abduction deficit without nystagmus. Adduction and convergence were normal. Sensation in the distribution of the first division of the trigeminal nerve was absent on the right and decreased on the left. Sensation in the distribution of the second and third divisions was normal bilaterally. There was a complete right and a severe but partial left facial paralysis. The left vocal cord had minimal motion on indirect laryngoscopy. Audiometric testing revealed a sensorineural hearing loss bilaterally. The sternocleidomastoid muscles and the tongue were normal. The rest of the neurological examination was unremarkable.

Comment

Twenty-one cases with CTA associated with ectodermal and/or mesenchymal structural defects (Group II) have been reported in the literature (Table 2). Ten of these had CTA as a part of Goldenhar's syndrome or oculoauriculovertebral dysplasia (OAVD). This condition is characterized by multiple congenital abnormalities involving the first and second branchial arches as well as vertebral and ocular anomalies (Budden and Robinson, 1973). The most essential features include preauricular tags, malformed pinnae, and epibulbar dermoids.

Three other patients have had the Möbius syndrome, namely congenital facial palsy associated with an abnormality of horizontal gaze (Henderson, 1939). More recently, 3 patients have been described with craniosynostosis, ataxia, hypertelorism, trigeminal anaesthesia, and segmental alopoecia (Gomez, 1979; López-Hernández, 1982). Both authors suggested that this represents a previously unrecognized neurocutaneous syndrome. The remaining 5 patients had a variety of associated anomalies including hypertelorism, imperforate anus, encephalocoele, alopoecia, cleft palate, and facial hypoplasia. These associated deficits are similar in both the OAVD and non-OAVD groups.

The extent of anaesthesia was strikingly different in this group as compared with the first. Only 1 of 10 patients with isolated CTA had a unilateral defect. In this second group, 10 of 21 patients were unilaterally affected. Also of interest was the fact that 8 out of 10 patients with OAVD had unilateral defects, while 9 out of 11 without OAVD had bilateral anaesthesia.

Further, the patients in the second group consistently had larger areas of sensory loss. In the first group, 40 per cent had normal facial sensation. Of the remainder, all had only the ophthalmic branch involved except one, who had anaesthesia in both the ophthalmic and maxillary distributions. In the second group only one patient is reported as having had normal facial sensation. All branches of the fifth nerve were involved in 6 cases, and only the first branch was effected in the others in whom this was reported.

TABLE 2 CLINICAL DATA FOR GROUP II CASES

	Author, sex/age (yr published)	*Ocular sensation*	*Facial sensation*	*Corneal ulceration (yr first noted)*	*Associated neurological features*	*Major somatic abnormalities*
1	Pillat M/7 (1949)	Bilat. absent	V1 bilat absent	NM	0	Bilat hypoplasia of hair and temporal muscles
2	Frayer M/5 (1955)	Bilat. absent	V1-3 bilat. absent	Bilat (7 mo)	Developmental delay, increased tendon reflexes, muscular atrophy	Imperforate anus, recto-vescicular fistula
3	Segall M/6 mo (1955)	RE absent, LE decreased	V1 bilat decreased	Bilat (6 mo)	Bilat facial weakness	Ear, thumb and vertebral anomalies, cleft lip and palate
4	Segall M/5 mo (1955)	Bilat absent	V1 bilat absent	LE (5 mo) RE (6 mo)	R torticollis	Vertebral and rib anomalies L facial and mandibular hypoplasia
5	Alajouanine *et al* F/4 mo (1930)	Bilat absent	V1-3 bilat absent	0	Bilat V1 and V2 palsy	Bilat club feet
6	Pitner *et al* M/2 days (1965)	RE absent	R V1 absent	0	Bilat V1 and V2 palsy	Micrognathia, hypoplasia of facial musculature
7	Sugar F/3 (1967)	Bilat absent	V1 bilat absent	Bilat (?)	Bilat facial weakness	Hemifacial microsomia, harelip, cleft palate, OAVD
8.	Bijsterveld M/12 (1969)	LE decreased	Normal	0	Abnormal EEG	Mandib hypoplasia, OAVD
9	Bowen *et al* F/1 mo (1971)	LE decreased	NM	0	Anophthalmos	Cleft palate, mandibular hypoplasia, rectovaginal fistula, imperforate anus, OAVD
10	Bowen *et al* F/6 mo (1971)	RE absent	NM	OD	NM	Bifid uvula, abnormal thumb, R facial hypoplasia, OAVD
11	Bowen *et al* M/19 mo (1971)	LE absent	NM	LE	NM	Thumb, ear and facial anomalies, hypertelorism, OAVD
12	Baum and Feingold ?/2 (1973)	LE absent	NM	LE	NM	OAVD
13	Budden and Robinson M/4 (1973)	LE absent	NM	LE	Bilat Duane's syndrome, bilat. sensorineural hearing loss	OAVD
14	Goldhammer and Smith M/2 (1975)	RE absent	NM	0	Megalopapilla RE	Preauricular nodules, hypertelorism, basal encephalocoele, cleft lip and palate
15	Aleksic *et al* F/2 5 (1975)	R anophthalmos	R V1-3 decreased	0	Decreased facial movement, anophthalmos	Cleft palate, OAVD
16	Mohandessan and Romano M/2 (1978)	Bilat decrease	V1 bilat markedly decreased	Bilat	Esotropia	OAVD
17	Gomez F/4 75 (1979)	Bilat absent	V1-3 bilat. absent	Scarring and ghost vessels of interstitial keratitis	Ataxia, incr tendon reflexes, bilat V2 palsy, esotropia, and motor V	Maxillary hypoplasia, hypertelorism, occipital alopoecia
18	López-Hernández F/10 (1982)	Bilat	V1-3	Bilat clouding	Ataxia, mental retardation	Midfacial hypoplasia, hypertelorism, focal alopoecia, abnormal ears, towerlike skull
19	López-Hernandez F/11 (1982)	Bilat	V1-3	Bilat clouding	Ataxia, mental retardation	Towerlike skull, focal alopoecias, midfacial hypoplasia, hypertelorism, abnormal ears and digits
20	Fiore *et al* M/13 (1983)	LE anophthalmos RE	NM	LE	Anophthalmos RE	OAVD
21	Rosenberg F/4 (1984, this paper)	RE absent, LE decreased	R V1 absent, L V1 decreased	RE (5 mo)	Bilat V1, V2 palsy, pectoral hypoplasia	Occipital encephalocoele

LE = left eye, RE = right eye, NM = not mentioned, OAVD = oculoauriculovertebral dysplasia

Corneal ulceration was less prominent in this group, although perhaps this was an artificial difference. These patients in general presented at a much younger age because of the associated abnormalities, and all patients without ulceration were under 24 months of age. Longer follow-up may have revealed a similar high incidence of corneal ulceration.

Case 3

The patient, a female aged 22 months, was noted immediately after an uneventful delivery to have a complete right facial palsy. Shortly thereafter she was found to have an exotropia of the left eye and an inability to gaze to the right. Examination at 22 months showed no evidence of corneal ulceration. Extraocular motility was severely affected. In primary position the left eye had a tendency to be exotropic, but could be voluntarily brought to the midline. With attempted gaze to the left there was good abduction of the ipsilateral eye associated with a small amplitude nystagmus. The right eye had little to no adduction. With attempted right lateral gaze there was no visible movement of either eye past the midline. Doll's head manoeuvre and ice water calorics confirmed the presence of a 'one and a half' syndrome. Convergence was well performed as were upward and downward gaze. There was no evidence of retraction with adduction of either eye. Forced ductions were normal. The fifth cranial nerve had normal motor function, but there was a marked decrease in the child's response to pin prick in the distribution of the first and second division of the trigeminal nerve on the right side. Corneal sensation was absent on the right, but normal on the left. There was no voluntary motion in the distribution of the right facial nerve, although the left was normal. The rest of the cranial nerves and neurological examination were unremarkable. Auditory evoked responses, CT cranial scans and EEG were normal.

TABLE 3 CLINICAL DATA FOR GROUP III CASES

Author, sex/age (yr published)	*Ocular sensation*	*Facial sensation*	*Neurological features*
1. Bernhardt M/5 mo (1890)	Absent R	V1-3 decreased on R	R V1, V2
2. Rosenberg F/22 mo (1984, this paper)	Absent R	V1-2 decreased on R	R gaze palsy, R internuclear ophthalmoplegia, R V2

Comment

There is only one other case in the literature of congenital sensory loss on the face associated solely with other neurological abnormalities and no evidence of somatic malformation (Table 3). These constitute Group III. Bernhardt (1890) described a very similar case of a young girl without systemic abnormalities, who had numbness of the right side of her face as well as ipsilateral sixth and seventh nerve paralysis. Neither girl developed corneal ulceration during the period of follow-up.

DISCUSSION

The aetiology of the sensory loss in these patients has been unclear because of the small number of post-mortem examinations that have been performed. Further, patients with vastly different clinical presentations have been assumed to have the same aetiology (Hewson, 1963). The differing clinical and epidemiological characteristics of each group as defined here, however, strongly support the idea that the groups should be considered as separate entities, most probably with separate aetiologies.

To date most authors have assumed that patients with isolated CTA had a primary hypoplasia of the trigeminal nuclei. Supporting this hypothesis has been the consistent lack of any associated neurological or mesoectodermal abnormalities. No autopsy material is available, however, on any of the patients in this group. It is difficult to conceive of a destructive lesion involving the sensory fibres of the trigeminal nerve bilaterally without interfering with any intervening structures. It is therefore again assumed, pending future autopsies, that these patients have a primary hypoplasia of the structures of the hindbrain involving the trigeminal nuclei.

The second group is more diverse. As more patients are reported it will probably come to be recognized as consisting of several different subtypes. The differing proportions of unilateral *versus* bilateral anaesthesia in those with OAVD compared with those without are suggestive of this. Nevertheless, the common prominent somatic abnormalities in all patients of this group suggest that an injury early in embryogenesis gives rise to abnormalities both of the mesodermal and ectodermal structures.

Pitner *et al.* (1965) presented the only complete autopsy examination in a patient of this group. He reported a patient who died with Möbius syndrome associated with anaesthesia of the first and second divisions of the fifth nerve. He found the cranial nerve nuclei to be normal. The peripheral muscles were severely abnormal, providing strong evidence in favour of a primary mesodermal dysplasia.

Aleksic *et al.* (1975), in contrast, studied a patient with CTA in association with OAVD and found aplastic fifth and seventh nerve nuclei ipsilaterally. He concluded that the abnormality was a primary hypoplasia of these structures. However, no peripheral tissue was examined and no electrophysiological studies were performed during life to assess the state of the peripheral tissues of the face.

These reports appear contradictory and, as mentioned, patients with OAVD may have a different pathology than other patients of this group. However, the conclusion of Aleksic *et al.* that OAVD is due to a primary neural aplasia cannot be accepted without an examination of the peripheral tissues. It has been known for some time that developmental lesions primarily involving mesenchymal tissue can lead to secondary neural dysplasia and, similarly, that malformation of the neural elements can lead to a secondary defect of mesenchymal tissue (Leszynsky, 1897).

Thus autopsied material showing both neural and mesodermal structures will be needed to establish the true aetiology in these cases.

The nature of the pathology in the third group seems more clear. Both patients showed evidence of a focal prenatal destructive process in the brainstem. The post-mortem examination of Bernhardt's patient (1890) revealed a circular softening in the right pons extending to the right mesencephalon, destroying the inferior colliculus and the lower portion of the superior colliculus. The cranial nerve nuclei were stated to be normal.

Although there is no pathological confirmation of the aetiology in the case presented here, the clinical syndrome of a gaze palsy associated with an internuclear ophthalmoplegia is sufficiently specific to give further support to this hypothesis. The association of these two findings allows the lesion to be localized to a small area in the mid- to lower pontine tegmentum (Wall and Wray, 1983). The accessory findings in our case are easily explained by a slightly expanded lesion involving the facial nerve or nucleus and the spinal tract or nucleus of the fifth nerve. As it implicates axons of a white matter tract (the right medial longitudinal fasciculus) without involvement of its cells of origin (the left abducens nucleus), it cannot represent a primary aplasia of structures as has been suggested for the first group. Rather it must be the result of a focally destructive process in the brainstem, as was Bernhardt's case (1890). The unilaterality of the process suggests a vascular aetiology, but in future cases the lesion may be shown to be secondary to other causes.

Despite this wide spectrum of associated features, some generalizations as to the clinical presentation and course can be made. The sensory deficit may be an isolated abnormality, or a part of a complex neurological syndrome with multiple somatic abnormalities. It may be asymptomatic and diagnosed only on examination, but it will usually present as either neuroparalytic keratitis or frank corneal ulceration. This problem is thought to result from a loss of the protective blink reflex, the afferent portion of which is mediated through the first division of the fifth nerve.

Although the sensory loss is present from birth, the age of onset of the ocular symptoms in all three groups was typically between 8 and 12 months. It has been suggested that this is due to the change in the sleeping habits of infants. As they get older and require less sleep, the eyes are exposed to the air for much greater periods of time (Segall, 1955). The condition tends to be benign, with few patients being left with marked visual loss secondary to corneal scarring.

Males and females are affected equally. The cornea and the conjunctiva are affected in all patients, and are the only areas of involvement in about 50 per cent of cases. This percentage varies significantly from group to group. When the face is involved, the distribution of the ophthalmic division of the trigeminal nerve is most often the only area affected. In other patients, however, sensation is abnormal over the entire face.

When corneal anaesthesia, with or without ulceration, is found as part of a more generalized disorder (e.g. the OAVD or Möbius syndromes), differential diagnosis is not a problem. If, however, it presents as an isolated finding, several other congenital and acquired conditions must be considered. Of the congenital conditions, the most common is the Riley-Day syndrome or familial dysautonomia. These patients are frequently of Jewish ancestry. Corneal ulceration occurs in about 30 per cent. They also have a general reduction in pain sensibility. Other problems include excess sweating, drooling, paroxysmal hypertension, problems with swallowing and absent tear secretion.

Congenital anhidrotic ectodermal dysplasia may be either an X-linked or autosomal dominant condition with abnormal hair and teeth, absent sweating and tearing, and cataracts. Corneal ulceration is relatively rare.

Acquired defects such as lagophthalmic keratitis, cerebellopontine angle mass, superior orbital fissure mass, and vitamin A deficiency can rarely also present with corneal abnormalities, and should be considered before concluding that the problem is due to CTA.

Treatment is required in those patients that have clinically significant corneal lesions. Patching is usually sufficient, but suturing the lid may be required. As the child grows, the corneal changes usually become less severe, and seem to heal more easily. Although corneal sensation never returns, it is assumed that this is due to the child learning to protect itself from possible damage to the eye using clues other than sensation.

ACKNOWLEDGEMENT

The opinions expressed are those of the author and do not necessarily reflect the views of the US Air Force or the Department of Defense.

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(*Received November 8, 1983. Revised April 10, 1984*)

Brain (1984), **107**, 1083-1094

COGNITION AND THE BASAL GANGLIA

SEPARATING MENTAL AND MOTOR COMPONENTS OF PERFORMANCE IN PARKINSON'S DISEASE

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SUMMARY

Central to the concept of subcortical dementia is the implication that the increased response latencies, which distinguish the syndrome, are due to a slowing of thought processes. The term 'bradyphrenia' has been applied to this presumed slowing of thought in Parkinson's disease and implies (1) that increased response latencies are not strictly motoric but are due to slowed information processing, and (2) that the mental slowing is analogous to the bradykinesia observed in the motor domain and, hence, attributable to dysfunction of dopaminergic basal ganglia mechanisms. The current study attempts to validate this definition of bradyphrenia by seeking a slowing of thought in Parkinson's disease which can be linked directly to bradykinesia. Six parkinsonian patients with end-of-dose akinesia were studied in three experiments which allowed separation of the speed of specific cognitive operations from the speed of motor responses. Serving as their own controls, they were tested both during the parkinsonian 'off' state, and when bradykinesia was alleviated by drug therapy. Four additional patients with newly diagnosed Parkinson's disease were studied before and following successful treatment with L-DOPA/carbidopa. The first experiment measured the rate of memory scanning, the second examined orientating of attention in the visual fields, and the third measured the time required to prepare a manual movement. The results show that overall reaction time increased when patients were in the untreated state, but without a concomitant slowing of purely cognitive components. The slowing of thought often reported in Parkinson's disease does not necessarily accompany bradykinesia and thus may not be related to dopaminergic dysfunction. These findings emphasize the need for caution in inferring a slowing of thought from increased response latencies in subcortical disorders.

INTRODUCTION

Reports that performance on psychometric tests is often impaired in Parkinson's disease (Riklan and Levita, 1969; Beardsley and Puletti, 1971; Reitan and Boll, 1971; Loranger *et al.*, 1972*a*; Riklan *et al.*, 1976; Mayeux *et al.*, 1981; Pirozzolo *et al.*, 1982; and that it may improve with L-DOPA treatment (Beardsley and Puletti, 1971; Marsh *et al.*, 1971; Loranger *et al.*, 1972*b*; Bowen *et al.*, 1975; Delis *et al.*, 1982), have

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stimulated speculation concerning the mechanisms whereby the basal ganglia may modulate higher mental processes. The concept of 'subcortical dementia' has been introduced, which links subcortical lesions to a 'slowing of thought' (Albert *et al.*, 1974; Albert, 1978). The term 'bradyphrenia' (Wilson, 1954) has been applied to this presumed slowing of thought in Parkinson's disease and implies (1) that increased response latencies are not strictly motoric but are due to slowed information processing, and (2) that the mental slowing is analogous to the bradykinesia observed in the motor domain, and hence is attributable to dysfunction of dopaminergic basal ganglia mechanisms.

There is evidence that information processing may be slowed in some parkinsonian patients. Wilson *et al.* (1980) found a slowing of 'high speed memory scanning' in older individuals with this disorder. Hansch *et al.* (1982) demonstrated an increased latency for the P_{300} component of the event-related potential in an auditory discrimination task. While both these studies provide evidence for a 'slowing of thought processes', neither examined its relationship to bradykinesia or to its improvement with drug therapy.

The current study attempts to crystallize and validate the concept of bradyphrenia by seeking a slowing of thought process in Parkinson's disease which can be linked directly to bradykinesia. It employs techniques which make it possible to measure changes in the speed of motor performance separately from the rate of information processing (Posner, 1978), and examines both concurrently in three cognitive tasks: memory scanning (Experiment 1), shifts of visual attention (Experiment 2), and preparation for manual movements (Experiment 3).

SUBJECTS AND METHODS

Ten patients with idiopathic Parkinson's disease were studied in three reaction time (RT) experiments. Each was studied when experiencing parkinsonian symptoms and also when these symptoms were alleviated by drug therapy.

Four patients were tested before receiving any drug therapy for Parkinson's disease, and retested several weeks after their symptoms had been successfully treated with L-DOPA/carbidopa. These included 3 women and 1 man, ranging in age from 66 to 75 years (average 71). Two were thought to have symptoms of early dementia.

Six male patients, age 33 to 70 years (average 58) with late levodopa failure were also studied. They had frequent clinical fluctuations throughout the day with periods of nearly normal motor function during 'on' phases, alternating with 'off' periods during which their parkinsonian symptoms became quite severe at the end of each drug dosage period. The clinical data for these patients are given in Table 1, including their L-DOPA/carbidopa schedule reflecting the periodicity of their 'on-off' cycles.

In all 6 patients with late L-DOPA failure, bradykinesia was the cardinal symptom during 'off' periods. Although a gradual end-of-dose 'wearing off' was most common in all 6, 3 (Cases 1, 4 and 5) occasionally had abrupt 'off' reactions. All had some degree of resting tremor during their periods but in none was it severe or disabling. All 6 of these patients had variable degrees of dyskinesia during their 'on' periods. None of these 6 patients was clinically demented. All were bright and articulate in conversation and remained active and independent.

Each of the 6 patients with late levodopa failure and end-of-dose akinesia were studied in 3 to 10 separate sessions on as many days over a period of several months. During each session a patient spent four to eight hours in the laboratory. An attempt was made to test the patient in all three experiments while both on and off the effects of medication at least once in each session, and the order of experiments was randomized. Usually patients had one or more 'on-off' cycles during a daily session. An effort was made to counterbalance sessions so that on some days the patients started the tests while on the effects of medication, while on other days they started the session while in an 'off' state. On some occasions, the patients continued to take their medications on their usual schedule throughout these sessions. Frequently, however, a patient would agree to delay a given dose for an hour or two so that he could become or remain symptomatic for sufficiently long to be tested in a given experiment while bradykinetic.

Throughout each session, the status of drug effect was assessed in different ways. Before each experiment, the subject was asked to give a subjective impression as to whether he was poorly or well controlled by his medication, or somewhere between. Neurological examinations assessed bradykinesia and rigidity to judge on clinical grounds whether again the patient was poorly or well controlled by the drug, or somewhere between. In addition, several perceptuomotor tasks were used to monitor the state of the patient's motor system. Handwriting was examined (both for speed and micrographia) and subtests of the MacQuarrie Test for Mechanical Abilities were also used.

In all these patients, the difference between 'on' periods and 'off' periods was quite evident clinically; disability was obvious during 'off' periods, while spry movements with dyskinesia were present when 'on'. Four patients were rated clinically by a psychologist and laboratory technician as well as by the neurologist who rated all 6. There was good reliability between raters of 'off' and 'on' periods. All clinical rating was done without knowledge of RT results. Although examiners were usually aware of the time that medication was taken, their rating as to whether a patient was designated as being 'on' or 'off' was based on objective clinical findings. Whenever the patient's clinical state changed during an experimental block (or if he felt he was in a transition state), the data were excluded from analysis.

During the remainder of this paper, the results from the 6 patients with daily fluctuations are discussed as being from 'on' or 'off' periods base on clinical ratings. The terms 'before-after' will be used to refer to the 4 newly diagnosed patients who were tested before receiving any treatment for Parkinson's disease, and again after L-DOPA/carbidopa. The term 'drug-alleviated state' is used to refer to 'on' and 'after' drug states together, while 'unalleviated state' refers to 'off' and 'before' together. All 6 of the 'on-off' patients were studied in all three experiments. All 4 of the 'before-after' patients were studied in Experiments 1 and 3; only 3 of the 4 were studied in Experiment 2.

In the three experiments described below, the patient sat comfortably facing a cathode ray tube (CRT) screen and was required to make responses to stimuli presented on the screen as rapidly and accurately as possible. The first experiment required a choice reaction key press response to a number

TABLE 1 MEDICAL BACKGROUND OF SIX PATIENTS WITH END-OF-DOSE AKINESIA

Patient	*Age (yrs)*	*Duration of illness/L-DOPA (yrs)*	*L-DOPA/carbidopa*		*Other therapy*
			No. of 250/25 tabs	*Frequency (h)*	
1	67	20/11	½	1–½	a, d
2	63	8/8	½ or 1	2	t
3	60	16/11	½	2	t
4	33	6/4/2*	1	3	b
5	54	14/12	½	2	a
6	70	7/4	1–½	2	—

* Right thalamotomy. a = amantadine; d = diphenhydramine; t = trihexyphenidyl, b = benztropine.

appearing on the screen, based on whether that number had just previously been seen; the second experiment involved a simple key press response to a target appearing randomly either to left or right of fixation; the third experiment required a choice reaction time response in which a handle was moved either to left or right in response to a peripheral target appearing to left or right of fixation.

For each experiment, median reaction time for each subject was calculated for each condition. These data were subjected to a repeated measures analysis of variance which included, as a between groups factor, a comparison of the two groups, namely 'on-off' patients and 'before-after' patients. Within groups factors always included the clinical drug state (drug-alleviated *vs* unalleviated). Thus RT indexed the effect of drug state on motor function. The analysis also examined interactions between drug state and variables such as set size or validity to determine if the speed of performing the specific cognitive operation being studied in the experiment was different in the two drug conditions. Oral and written informed consent was obtained from each patient for the experimental procedures.

EXPERIMENT 1. SCANNING OF SHORT-TERM MEMORY

In the first experiment, we reexamined the issue of 'high speed memory scanning' in Parkinson's disease studied by Wilson *et al.* (1980). In that study, a variation of the choice reaction time paradigm developed by Sternberg (1966) was used to measure the rate at which short-term memory is scanned mentally. In this kind of task, subjects are given a list of digits to remember. They are then immediately shown a single digit and are required to make a choice reaction time response as to whether or not the number was a member of the previously memorized set. The longer the set, the longer it takes an individual to decide whether a target was or was not a member of that set. In general, for young subjects there is approximately a 30 ms increase in reaction time for each additional number in the set the subject must scan to make his/her decision. Reaction time is measured for different set sizes and the resulting slope serves as a measure of the speed of scanning memory.

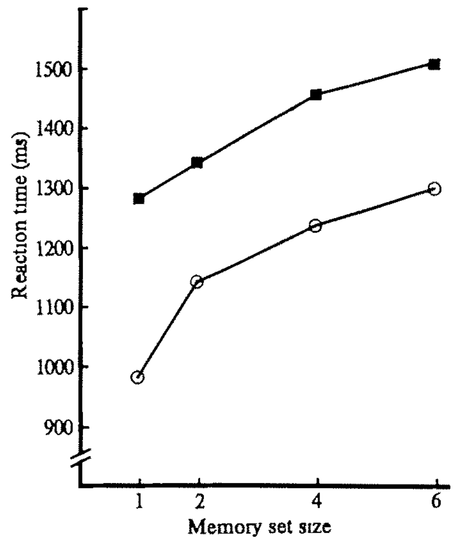

FIG 1. Mean reaction time as a function of memory set size for Experiment 1 (memory scanning) in alleviated o——o and unalleviated ■——■ drug states.

TABLE 2. PERCENTAGE ERROR RATES IN EXPERIMENT 1

	Memory set size			
	1	*2*	*4*	*6*
Unalleviated by drug therapy	4	5	6	12
Alleviated	2	5	5	12

Method

For our task, subjects were shown a list of 1, 2, 4 or 6 digits presented simultaneously on a CRT screen and were given 0.5 s per item to read and remember the list. The number of digits in the set to be recalled varied randomly from trial to trial. One second after each list terminated, subjects were shown a single target digit and were required to report as quickly a possible whether or not that item was a member of the list by pressing either a 'yes' or a 'no' key. After each decision was made, a new list of target numbers was presented.

Results

Median RTs and error rates were computed for each patient. The mean of the median RTs for all 10 patients is shown as a function of set size and drug alleviation in fig. 1. Table 2 shows that error rates were not different between alleviated and unalleviated conditions. Inspection of fig. 1 indicates that patients are faster when alleviated. RTs also increase with set size as is usual in this task. These findings are confirmed by the results of an analysis of variance of RTs which involved one between factor ('on-off' group *vs* 'before-after' group) and two within factors (set size and alleviation). All factors which are significant are shown in Table 3. Both alleviation and set size show significant effects. In addition, there is a significant interaction between group and alleviation which shows that the 'before-after' group

TABLE 3 VARIABLES SHOWING DIFFERENCES BETWEEN CONDITIONS IN THE THREE EXPERIMENTS[1]

	Variable		
	DF	*F*	*P*
Experiment 1. (Memory scan)			
Drug	1, 8	10.7	< 0.011
Set size	3, 24	5.1	< 0.006
Experiment 2. (Covert orientating)			
Validity	1, 7	38.81	< 0.001
Interval	3, 21	11.04	< 0.001
Experiment 3. (Preparing a manual movement)			
Drug	1, 6	9.6	< 0.02
Validity	1, 6	45.6	< 0.001
Interval	3, 18	33.3	< 0.001

[1] $P < 0.05$.

has a smaller benefit from drug therapy than the 'on-off' group. Much of this interaction is due to one 'before-after' patient who showed only a small decrease in RT after treatment. Another 'before-after' patient, with a high error rate (16%), showed a negative effect of set size on RT which resulted in a tendency towards a triple order interaction of group × set size × alleviation ($P = 0.068$). This trend suggested a smaller set size effect (i.e. a *faster* rate of memory scanning) for members of the 'before-after' group *before* receiving the drug. However, the major result of this study is that treatment has a large overall effect on reaction time but no interaction with set size that would indicate a speeding of cognition when treated.

When these patients were used as their own controls, we found no evidence that bradykinesia was accompanied by a slowing of memory scanning. The slope relating RT to set size in the range from 2 to 6 items is about 40 ms per item, which is well within the normal range for this age. Wilson *et al.* (1980) compared the rate of high speed memory scanning for a group of 'nondemented' parkinsonian patients with age-matched controls. They interpreted their results as supporting a bradyphrenia hypothesis. However, they found a slowing of memory scanning only for their older parkinsonians; the younger patients compared favourably with controls. If bradyphrenia in memory scanning occurs in Parkinson's disease, it is not universal. Moreover, Wilson *et al.* (1980) did not link any slowing of information processing to measures of bradykinesia nor to drug treatment. Our results do not suggest any such relationship, and do not validate the concept of bradyphrenia in any sense that can be related to bradykinesia or to dopaminergic dysfunction.

EXPERIMENT 2. COVERT ORIENTATING OF ATTENTION IN THE VISUAL FIELD

Because the literature emphasizes visuospatial deficits in parkinsonian patients (Reitan and Boll, 1971; Danta and Hilton, 1975; Mayeux *et al.*, 1981; Mortimer *et al.*, 1982), the second experiment examined covert orientating of attention in the visual field. We have used this paradigm in normals to show that covert shifts in attention can occur independently from overt movement of the head and eyes; and that parietal lesions, and midbrain degeneration in progressive supranuclear palsy, affect covert orientating (Posner *et al.*, 1982, 1984). The notion that the basal ganglia may be involved in mediating this kind of attentional process 'preparatory to a motor performance oriented to the environment' was suggested by Denny-Brown and Yanagisawa (1976) on the basis of lesion experiments in monkeys. Hassler's (1978) stimulation experiments also implicated the basal ganglia as 'directing attention to the contralateral side'. Experiments 2 and 3 were designed specifically to test this hypothesis.

Method

Subjects fixated a central cross and were asked to press a single key rapidly whenever they saw an asterisk which appeared randomly either 10 deg to the left or right of centre. Each trial began with a cue

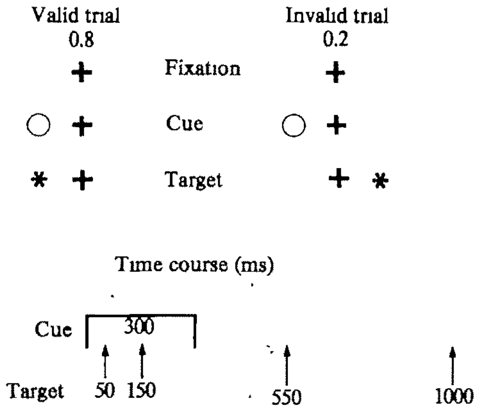

FIG. 2. Experimental design for Experiments 2 and 3 The top panel shows the sequence of the visual display for the two trial types. A fixation stimulus is followed by a peripheral cue (brightening of the box). After a variable interval a target appears 80 per cent are within the cued box = valid cue condition; 20 per cent appear opposite the box = invalid cue condition. The lower panel indicates the intervals between onset of the cue and the onset of the target used for Experiment 2. For Experiment 2, patients responded to the target with a simple finger key press response. For Experiment 3, patients rapidly moved a heavy lever in the direction of the target.

which was the brightening of one of two peripheral boxes indicating to the subject where to expect the target to appear (fig. 2). The cue was valid (i.e., the target appeared within the cued box) 80 per cent of the time, while on 20 per cent of the trials the cue was invalid (i.e., appeared opposite the cue). The cue onset preceded the appearance of the target by 50, 150, 550 or 1,000 ms and remained present for 300 ms. The target remained present until the subject responded, or for 5,000 ms. A longer reaction time following invalid cues than following valid cues was used to infer that the subject had sufficient time to shift attention to the cue during the interval between cue and target.

Results

The median RTs were computed for each patient for each condition of the experiment. The means of the medians for all 9 patients tested in this experiment are shown in fig. 3. There is a very clear effect of validity with valid trials (solid lines)

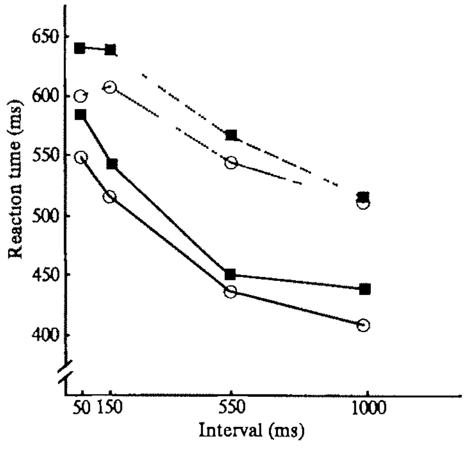

FIG. 3 Mean reaction time as a function of interval between cue onset and target for Experiment 2 (covert orientating). Alleviated by drug therapy valid o——o, invalid o· · ··o. Unalleviated: valid ■——■; invalid ■·····■.

faster than invalid trials (dotted lines). RTs generally decline with increasing interval. The RTs under the alleviated condition tend to be faster than under the unalleviated conditions. An overall analysis of variance of the RTs involved 1 between group factor ('on-off' *vs* 'before-after') and 3 within group factors (alleviation, validity and interval). The factors which are significant are shown in Table 3. This study does not show a significant effect of drug treatment on reaction times, although they are systematically in the direction of being faster in the alleviated condition as shown in fig. 3. Both validity and interval show the expected effects. There is no hint of any effect of treatment on the speed of covert orientating of attention. These patients show clear validity effects by 50 ms just as do normal subjects (Posner *et al.*, 1982) and they show the same pattern both when motor symptoms are alleviated and unalleviated. In summary, this experiment gave no indication that parkinsonian patients are slow in shifting attention in the visual field.

EXPERIMENT 3. PREPARATION FOR VOLUNTARY MANUAL MOVEMENTS

If there is a 'bradyphrenia' or slowing of thought processes in Parkinson's disease, it would be most reasonable to expect to find it for those cognitive processes involved in the preparation of voluntary movement. The third experiment measured the latency of parkinsonians to prepare a motor set in anticipation of making a voluntary manual movement.

Method

The experiment was similar to Experiment 2 in that the display used was identical; however, a choice reaction time response was required and the patients were asked to move a heavy lever either to the left or right in response to the peripheral target. In this experiment, therefore, the peripheral cue preceding the target instructed subjects which direction of movement to prepare. A slower RT for invalid than for valid cues at any given warning interval was assumed to indicate that the individual had had sufficient time to prepare a motor set during that interval.

All 10 patients were studied in this experiment. Both hands were tested independently except for one of the 'on-off' patients who could only do the test with his less affected (left) hand. Cue to target intervals were 50, 200, 350 and 500 ms, except for two 'on-off' subjects in whom the 50 ms interval was omitted. (They were probed at 200, 350, 500 and 1,000 ms.)

Results

Data from the 8 subjects in whom complete data were available are shown in fig. 4. Reaction times were systematically slower in the unalleviated state. RT to valid targets was faster than for invalid targets, and RT decreased with longer intervals for both alleviated and unalleviated conditions. The effect of validity was similar in the alleviated and unalleviated conditions, and was present at the 50 ms warning interval in both. Thus, although the unalleviated subjects had slower reaction times overall, they were no slower in preparing mentally to move as shown by the robust validity effect 50 ms following the cue.

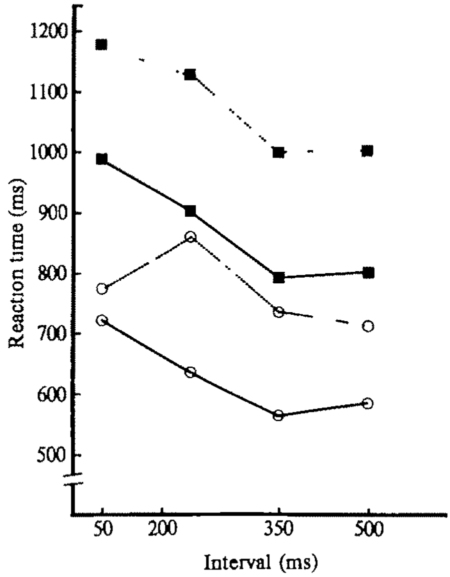

FIG. 4 Mean reaction time as a function of interval between cue onset and target for Experiment 3 (preparing a manual movement). Alleviated by drug therapy: valid o——o; invalid o ···· o Unalleviated: valid ■——■; invalid ■ ··· ■

Table 3 shows that main effects of drug state (alleviated and unalleviated), validity, and interval were all significant. There were no significant interactions, and no differences between the two subject groups. There was a tendency for drug state to interact with validity ($P = 0.11$). However, since this tendency was due to a *smaller* validity effect at the 50 ms cue interval in the *unalleviated* drug state, it does not indicate a relative cognitive deficiency in the unalleviated state.

In summary, these results do not indicate that bradykinesia is accompanied by slowness in assembling a motor program in response to a preliminary cue to get ready to move. They do not exclude the possibility that bradykinesia may be due to a slowing in some later, executive stage of motor programming which can only be activated after the signal to begin the movement.

DISCUSSION

There is continuing controversy as to whether the basal ganglia are involved in human cognition (Cools *et al.*, 1981; Marsden, 1980, 1982). While the examination of mental function in patients with Parkinson's disease is, potentially, one of the most direct approaches to this problem, it is one which must be constrained by an appreciation for the anatomical, clinical and neurochemical heterogeneity of the disease. Some degree of coexisting cortical degeneration, varying from mild histological changes of Alzheimer's type to gross cortical atrophy, is nearly always present (Hakim and Mathieson, 1979; Boller *et al.*, 1980). Clinically, the severity of mental impairment also constitutes a spectrum from mild deficits found only on sensitive psychometric testing, to severe dementia (Pirozzolo *et al.*, 1982). Thus, the boundary between demented and nondemented patients is not clear; and we cannot be confident that subtle impairment found in apparently 'nondemented' parkinsonians is not related to coexisting cortical disease rather than to basal ganglia dysfunction.

More direct evidence for a role of the basal ganglia in cognition comes from studies which link specific mental deficits to cardinal motor symptoms such as bradykinesia (Mortimer *et al.*, 1982). The documentation of improved mental performance after successful drug therapy for bradykinesia, which has been demonstrated in numerous studies (Beardsley and Puletti, 1971; Marsh *et al.*, 1971; Loranger *et al.*, 1972*b*; Bowen *et al.*, 1975; Delis *et al.*, 1982) also seems to implicate a common neurochemical pathophysiology for both motor and mental symptoms caused by basal ganglia lesions.

Given this line of evidence, the concept of 'bradyphrenia' is an attractive one since it implies not only a common pathophysiology with bradykinesia, but also that the mental impairment is due to a slowness of thought processes, analogous to the slowing in the motor domain. Unfortunately, in most studies which have found improvement in mental function with L-DOPA, the tasks used experimentally did not permit the direct measurement of the speed of mental information processing independent of the speed of the motor responses from which mental activity was inferred.

The current investigation attempted to validate the concept of bradyphrenia as defined by the following criteria: (1) cognitive impairment in parkinsonians caused by a slowing of information processing; (2) which accompanies, but which is not caused by, slowness in initiating motor responses; and (3) which can be remediated by drug therapy concomitantly with improved motor function.

In all three of our experiments reaction time was consistently slower when patients were unalleviated by drug treatment. In the two choice RT experiments, the effect of drug state was significant. In the simple RT experiment, the effect of drug state did not achieve significance, although the clinical ratings in this experiment were the same, and the data were collected at the same time as in the two choice RT experiments. Our findings, therefore, suggest that choice RT responses may be more vulnerable to the effects of unalleviated Parkinson's disease than are simple RT responses.

The chief finding of this investigation is that these changes in motor function occurred without any evidence for cognitive slowing in any of the three experiments. Since we found no changes in the rate of information processing linked to bradykinesia or its alleviation by drug therapy, our results do not confirm the hypothesis that there is a 'bradyphrenia' or slowing of thought which can be attributed to the same basal ganglia disorder that causes slowness of movement.

It may be that mental impairment found in some parkinsonians is due to coexisting Alzheimer changes causing degeneration in the cerebral cortex and its cholinergic afferents from the substantia innominata (Hassler, 1965; Whitehouse *et al.*, 1983). This explanation does not address the question as to whether there may also be distinctive cognitive changes in Parkinson's disease which are due to lesions of the basal ganglia.

We cannot conclude from our findings that the slowing of cognition found by others (Wilson *et al.*, 1980; Hansch *et al.*, 1982) in Parkinson's disease is not due to dopaminergic insufficiency; only that it is not universal in Parkinson's disease nor obligatorily linked to bradykinesia. It is possible that bradyphrenia, as defined here, does occur in some parkinsonians who have substantial deficiencies in mesolimbic or mesocortical dopamine pathways. In our patients, a dopaminergic deficiency may have been restricted to the nigrostriatal system; or, in the case of our 'on-off' patients, that fluctuations in nigrostriatal dopamine may have occurred without, or out of synchronization with, mesolimbic/mesocortical dopamine changes.

Newer techniques of brain imaging and neurochemistry should make it possible to identify subpopulations of parkinsonian patients, and to isolate for study groups differing both in the anatomical involvement of subcortical and cortical structures (Sroka *et al.*, 1981) and in the distribution of subcortical neurotransmitter dysfunction (Wooten and Horne, 1982). Such advances will afford new opportunities to determine if, and how, the basal ganglia may contribute to higher mental processes.

ACKNOWLEDGEMENTS

This work was supported by funding from NIMH (1 RO3 MH 37748-01), the American Parkinson Research Foundation, the Murdock Charitable Trust, and the Medical Research Foundation of Oregon. We are grateful to Ms Gail Mauer for assistance in the preparation of the manuscript, and to Drs Robert S. Dow and Hubert Leonard who kindly referred patients to this study.

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(*Received April 26, 1983. Revised March 23, 1984*)

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PSYCHOPHYSICAL AND ELECTROPHYSIOLOGICAL APPROACHES TO THE PAIN-RELIEVING EFFECTS OF HETEROTOPIC NOCICEPTIVE STIMULI

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SUMMARY

The nociceptive flexion reflex (R_{III} reflex) and the concurrent subjective pain score elicited by right sural nerve stimulation at random intensities were studied in 10 healthy volunteers. A close relationship was found between the recruitment curves of the reflex and the pain score as a function of stimulus intensity. As a consequence, the threshold of the R_{III} reflex (T_r) and of pain sensation (T_p) were found to be almost identical (mean: 9.8 and 11.3 mA, respectively). Similarly, the threshold for obtaining a maximal reflex response (T_{mr}) was found to be very close to that for intolerable pain (T_{ip}): 33.5 and 35.1 mA, respectively.

These four parameters were studied before and during the immersion of the left hand into a heated thermoregulated waterbath at various temperatures (from 40 to 47.5° C). While nonnociceptive temperatures (40 to 44° C) were without effect, higher conditioning temperatures induced an increase in the four thresholds. In addition, a highly significant linear relationship was observed between the increase in these thresholds and the intensity of the conditioning stimulus in the 44 to 47.5° C range.

These four parameters were also studied before and during three other nociceptive conditioning stimuli: immersion of the left hand into a 6° C waterbath, 10 watts muscular exercise of the left hand performed under ischaemia and a painful (5.5 kg/cm^2) pinch applied on the nasal septum. These three conditioning situations induced a very significant increase of the four thresholds considered in this study with the greatest being observed during nociceptive cold applied to the left hand.

During all the conditioning situations, variations in T_r and T_p as well as in T_{mr} and T_{ip} were found to be linearly related. This indicates a close relationship between the effects of the conditioning nociceptive stimuli on the reflex and the related pain sensation.

These results suggest that the modulation of pain by heterotopic nociceptive stimuli can be explained at least in part by a depression in the transmission of nociceptive messages at the spinal level. They are discussed with reference to the counterirritation phenomena and common features with 'diffuse noxious inhibitory controls' (DNIC) are underlined.

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INTRODUCTION

Counterirritation phenomena, that is, the paradoxical pain-relieving effects of pain elicited from heterotopic body areas, have been known for centuries and most popular methods of practising medicine have included and still do include their therapeutic use (Wynn, 1947; Wand-Tetley, 1956; Le Bars *et al.*, 1984). Furthermore, painful electrical stimulation of the skin (Sarlandière, 1825; Trousseau and Pidoux, 1836–1839; Duchenne, 1855) has recently been reintroduced in the treatment of chronic pain (Melzack, 1975; Jeans, 1979) and has been described as 'hypoalgesia by hyperstimulation'. Along the same lines, intense cold ('ice massage') applied to the hand has been reported to relieve dental pain (Melzack *et al.*, 1980*a*) and related methods have been used for the treatment of muscular (Travell, 1952; Grant, 1964; Mennell, 1975) and low back pain (Melzack *et al.*, 1980*b*).

Surprisingly, the phenomena have not given rise to many investigations involving experimental pain in man (Duncker, 1937; Hardy *et al.*, 1940; Gammon and Starr, 1941; Parsons and Goetzl, 1945; Pertovaara *et al.*, 1982).

The first aim of the present study was to attempt to investigate these phenomena in a quantitative fashion. In addition, we have recently proposed (Le Bars *et al.*, 1979*b*) that inhibitory mechanisms occurring at the spinal level could be the neural basis for counterirritation phenomena. This hypothesis was tested in the present study by investigating the effects of heterotopic nociceptive stimuli upon a nociceptive spinal reflex (R_{III} reflex). The sural nerve was stimulated and both the R_{III} reflex and the simultaneously evoked sensation were recorded to allow the study of the effects of various conditioning nociceptive stimuli applied to the contralateral arm or nose of human subjects. This experimental protocol was chosen because the threshold of R_{III} reflex was previously found to be close to the threshold of pain sensation (Willer, 1977). The results demonstrated that both pain sensation and reflex activities can be reduced by all types of conditioning nociceptive stimuli used in this study. A preliminary report of this work has previously appeared (Le Bars *et al.*, 1983).

METHODS

The experiments were performed on 10 healthy volunteers (8 men, 2 women, 26 to 44 years old), carefully briefed and familiar with the experimental procedure. They gave their informed consent, according to the principles of the Helsinki convention. During the sessions, the subjects sat comfortably reclined in an armchair in order to obtain good muscular relaxation. The details of the method for stimulating the sural nerve and recording reflex activity from a knee flexor muscle have previously been fully described (Willer, 1977). In brief, the right sural nerve was stimulated at a rate of 0.25 Hz behind the lateral malleolus through a pair of surface electrodes, 2 cm apart on the degreased skin. The electrical stimulus consisted of a volley of 8 rectangular pulses (1 ms duration) delivered over 20 ms. Their intensity was varied randomly (*see below*) and was permanently monitored. Electromyographic reflex responses were recorded from the ipsilateral biceps femoris muscle, using a pair of surface electrodes on the degreased skin overlying the muscle (fig. 2A). These reflex responses were full-wave rectified, integrated (usual time window 100 ms, 80 ms after the stimulus onset) and expressed as percentages of the maximal control values.

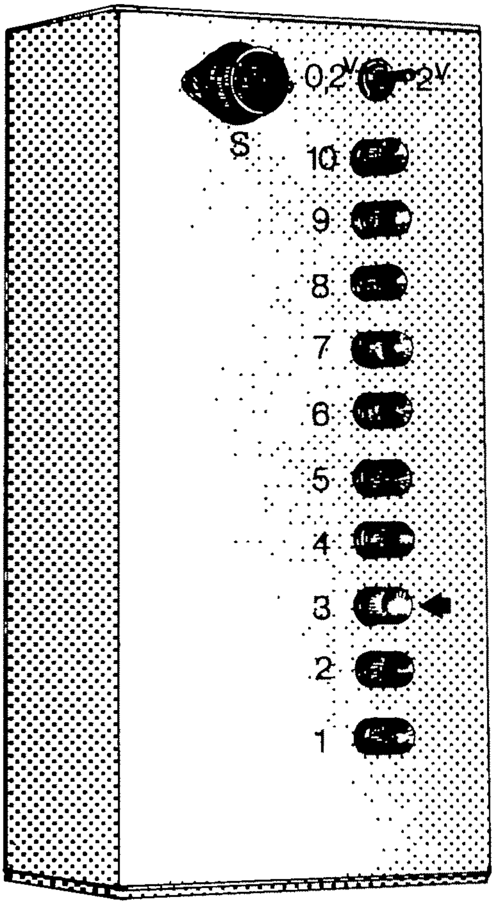

FIG. 1. Device used by the subjects for estimation of sensations elicited by the sural nerve stimulus The ten-level visual scale consists of ten potentiometers (S = output). The pain threshold is defined as level 3 (arrow) and intolerable pain as level 10 (*see text*). The device was manipulated by the right hand of the subject.

The subjective quality (tactile or painful) and intensity of the sensation elicited by the sural nerve stimulus were estimated by the subjects on a ten-level visual scale consisting of 10 switches (fig. 1). Each of these was connected to a potentiometer delivering a d.c. current from 0.2 V (level 1) to 2 V (level 10) by increasing 0.2 V steps. The pain threshold was defined as level 3. Thus the first two levels represented tactile sensations, while levels 4 to 10 corresponded to increasingly painful sensations from just above threshold to intolerable pain.

The electrical signals (reflex, sensation and stimulus intensity) were fed to a storage oscilloscope to allow the monitoring of the experiments, to a tape recorder, and to a computer for on-line digitization of data. Because of a technical breakdown, some data relating to the reflex responses could not be analysed.

The intensity of stimulation was delivered randomly while both the digitized nociceptive reflex and sensation were plotted against stimulus intensity *via* a computer program. As shown in fig. 2, both the reflex activity and subjective rating score increased linearly as a function of stimulus intensity within a limited range. This allowed the measurement of both pain and nociceptive reflex thresholds. For this purpose at least 20 x-y points were used for calculating the regression curves; for each curve, the significance of the regression coefficient (r) was always at $P < 0.01$.

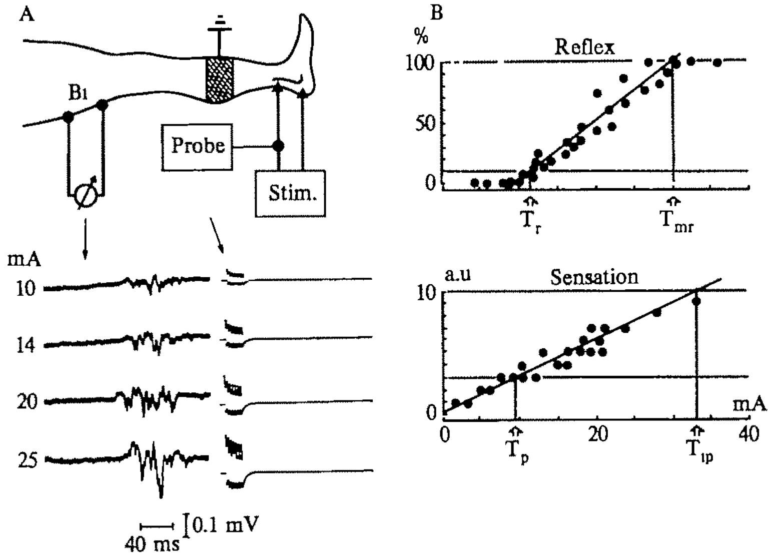

FIG. 2. A *Upper part*: experimental design for stimulating the sural nerve (Stim.), measuring the stimulus intensity (Probe) and recording reflex activity from the biceps femoris muscle (Bi). *Lower part*: example of recruitment of the nociceptive reflex (R_{III}) activity (*left*) as a function of stimulus intensity (*right*). B. *Upper part*: method for calculating the reflex threshold (T_r) and the threshold for obtaining a maximum reflex response (T_{mr}). *Lower part*: method for calculating the pain threshold (T_p) and the threshold for intolerable pain (T_{ip}) (*see text*; a.u = arbitrary units).

The reflex threshold (T_r) was defined as the abscissa corresponding to the intersection of the reflex linear regression curve with the 10 per cent ordinate line (upper fig. 2B). The threshold for obtaining a maximal reflex response (T_{mr}) was defined as the abscissa corresponding to the intersection of the reflex linear regression curve with the 100 per cent ordinate line (upper fig. 2B).

The pain threshold (T_p) was defined as the abscissa corresponding to the intersection of the sensation linear regression curve with the level 3 ordinate line (lower fig. 2B). The threshold for intolerable pain (T_{ip}) was defined as the abscissa corresponding to the intersection of the sensation linear regression curve with the level 10 ordinate line (lower fig. 2B).

The general experimental procedure consisted in the repetition of the protocol described above, before and during the application of a heterotopic conditioning stimulus.

The effects of conditioning noxious and nonnoxious heat stimuli applied to the left hand were studied on the pain sensation and nociceptive reflex elicited by stimulation of the right sural nerve. For this purpose, subjects were required to dip the hand, to a depth of 5 cm above the wrist, into an agitated thermoregulated waterbath for a time varying between 2 and 3 min. Several temperatures were tested in random order (40, 42, 44, 45, 46, 47, 47.5° C).

The effects of other modalities of noxious stimuli such as cold, noxious pinch and muscular pain were also studied using the following procedures. (1) For cold stimuli, subjects were required to dip the left hand into an agitated waterbath maintained at 6° C. (2) For muscle pain, subjects had to perform a 10 watts muscular exercise with the left forearm during ischaemic block of the arterial blood flow achieved by a pneumatic cuff placed around the middle of the left arm and inflated to 1.5 times the systolic blood pressure. (3) For a noxious pinch, a pressure of 4.5 kg/cm² was applied to a 15 to 20 mm² area of the nasal septum using a pair of forceps.

For a given subject, a maximum of 3 sequences were performed during any one session; the time between sequences consisted of a 20 min relaxation; each session lasted between 60 and 90 min. For each sequence, numerical data concerning the effects of the heterotopic stimuli upon the four parameters defined above were expressed as percentages of the control values. Global mean results were expressed in terms of percentage increases in thresholds. Paired t test and linear regression analysis were used for studying the significance of variations.

RESULTS

As described above, the experimental procedure consisted of sequences during which both the spinal nociceptive reflex (R_{III}) and the related subjective sensation elicited by the random stimulation of the right sural nerve were measured before and during the application of heterotopic conditioning somatic stimulation. The following sections consider in turn the characteristics of the unconditioned (control) response and their modification by conditioning stimuli.

Characteristics of Control Responses

The general characteristics of the control responses are illustrated with a typical individual example in fig. 2B. In this experiment, the threshold of the R_{III} response was 11.8 mA and the threshold of the maximal R_{III} response was 30.0 mA; note the linear nature of the intensity-response curve between these values. The corresponding curve obtained for subjective sensations exhibited a similar trend with 9.8 mA and 32.9 mA as thresholds for pain and intolerable pain, respectively. Such curves were generally very reproducible with minimal variations between sequences (*see* figs. 3 and 5, dotted lines).

The Table summarizes the mean reflex (T_r) and pain (T_p) thresholds for individual subjects and their corresponding thresholds for maximal reflex response (T_{mr}) and intolerable pain (T_{ip}). In 2 subjects, it was not possible to analyse the reflex activity because it was always contaminated with an EMG response related to

TABLE INDIVIDUAL MEAN (±SEM) CONTROL THRESHOLDS VALUES OBTAINED FOR THE 10 SUBJECTS

	Reflex			*Sensation*			*Reflex/sensation relationships*	
	T_r (*mA*)	T_{mr} (*mA*)	T_{mr}/T_r	T_p (*mA*)	T_{ip} (*mA*)	T_{ip}/T_p	T_p/T_r	T_{ip}/T_{mr}
Subjects	*m̄ SEM*	*m̄ SEM*		*m̄ SEM*	*m̄ SEM*			
1	10.3±0.3	38.2±2.8	3.7	8.7±1.0	29.5±3.0	3.4	0.84	0.77
2				8.8±0.2	28.9±1.8	3.3		
3	8.5±0.3	30.1±3.1	3.5	10.1±0.7	30.6±1.7	3.0	1.18	1.01
4	10.0±0.4	21.9±2.1	2.2	10.3±1.1	31.9±2.2	3.1	1.03	1.46
5	8.9±0.3	32.0±2.7	3.6	10.4±0.7	29.0±0.9	2.9	1.16	0.90
6	9.6±0.2	31.0±2.9	3.2	10.5±1.0	33.7±2.6	3.2	1.09	1.09
7				12.4±0.3	31.4±1.4	2.5		
8	10.1±0.1	38.8±2.1	3.8	12.4±0.9	38.2±3.3	3.1	1.23	0.98
9	10.4±0.4	37.8±3.2	3.6	13.2±0.8	49.4±5.6	3.7	1.26	1.31
10	10.4±0.4	38.0±3.0	3.5	15.8±0.6	49.0±3.6	3.1	1.51	1.27
m̄ ± SEM	9.8±0.3	33.5±2.1	3.4±0.2	11.3±0.7	35.1±2.5	3.1±0.1	1.16±0.07	1.10±0.08

T_r = nociceptive reflex threshold, T_{mr} = threshold of maximal nociceptive reflex response, T_p = pain threshold, T_{ip} = threshold for intolerable pain. *See text* for interpretation of ratios (T_{mr}/T_r, T_{ip}/T_p, T_p/T_r and T_{ip}/T_{mr}). Subjects are listed with reference to increasing values of T_p, the overall means are added on the lower line a jumping movement. An indication of the variation between sequences and between individuals can be obtained by considering the standard errors of the means (SEM) as indicated in the Table for each individual subject and for the whole group. Note that the variations both between sequences and between individuals were relatively low for T_r, slightly higher for T_p (two- to threefold) and much higher for T_{mr} and T_{ip} (approximately ten-fold). However, the mean intensity-response curves obtained with all the subjects for the reflex responses and the pain sensations were, overall, remarkably similar. On the one hand, the mean values for T_r and T_p were 9.8 ± 0.3 and 11.3 ± 0.7 mA, respectively, while on the other, T_{mr} and T_{ip} were found to be of 33.5 ± 2.1 and 35.1 ± 2.5 mA, respectively.

The similarity in the intensity-response curves can also be seen on the right of the Table which indicates the T_p/T_r and T_{ip}/T_{mr} ratios for individual subjects; note that most of these values are close to 1. The Table also shows that the threshold for obtaining a maximal reflex response was close to three times the reflex threshold (mean $T_{mr}/T_r = 3.4 \pm 0.2$). Similarly, the threshold for intolerable pain was also close to three times the threshold of pain sensation (mean $T_{ip}/T_p = 3.1 \pm 0.1$). Note again the relatively small variations between individuals.

As described in the following section, these intensity-response curves could be markedly influenced by various heterotopic nociceptive conditioning stimuli.

Effects of Heat Applied to the Hand

The responses described above were recorded before and during the immersion of the contralateral hand in a waterbath. As shown in fig. 3, which illustrates an individual example, the responses were modified in direct relationship to the conditioning temperature of the waterbath. At 42° C, neither the reflex nor the sensation recruitment curves were different from the controls. At 44° C there was a slight shift to the right for the reflex response curve while the sensation curve remained unchanged. The shift of the reflex curve is mainly due to a change in the slope, the T_r being unchanged. In contrast with 45, 46 and 47° C, both the reflex and the sensation recruitment curves were shifted to the right, with a maximal effect for the highest temperature. Note both the progressive increase in T_r, T_{mr}, T_p and T_{ip}, and the decrease in the slopes of the curves as a function of the temperature.

Data obtained for all the subjects are summarized in fig. 4, which shows the mean increase in threshold as a function of the conditioning temperature applied to the left hand. Note that moderate (nonnoxious) temperatures, in the 40 to 44° C range did not significantly modify the four parameters considered. In contrast, higher conditioning temperatures clearly induced an increase in the four thresholds. In addition, these increases were very significantly related to the intensity of the conditioning stimuli. This relationship was linear in the 44 to 47.5° C range (dotted lines). Higher temperatures were not tested because 47.5° C was the highest temperature that could be tolerated for a sufficient length of time to obtain the intensity-response curves (*see* Methods).

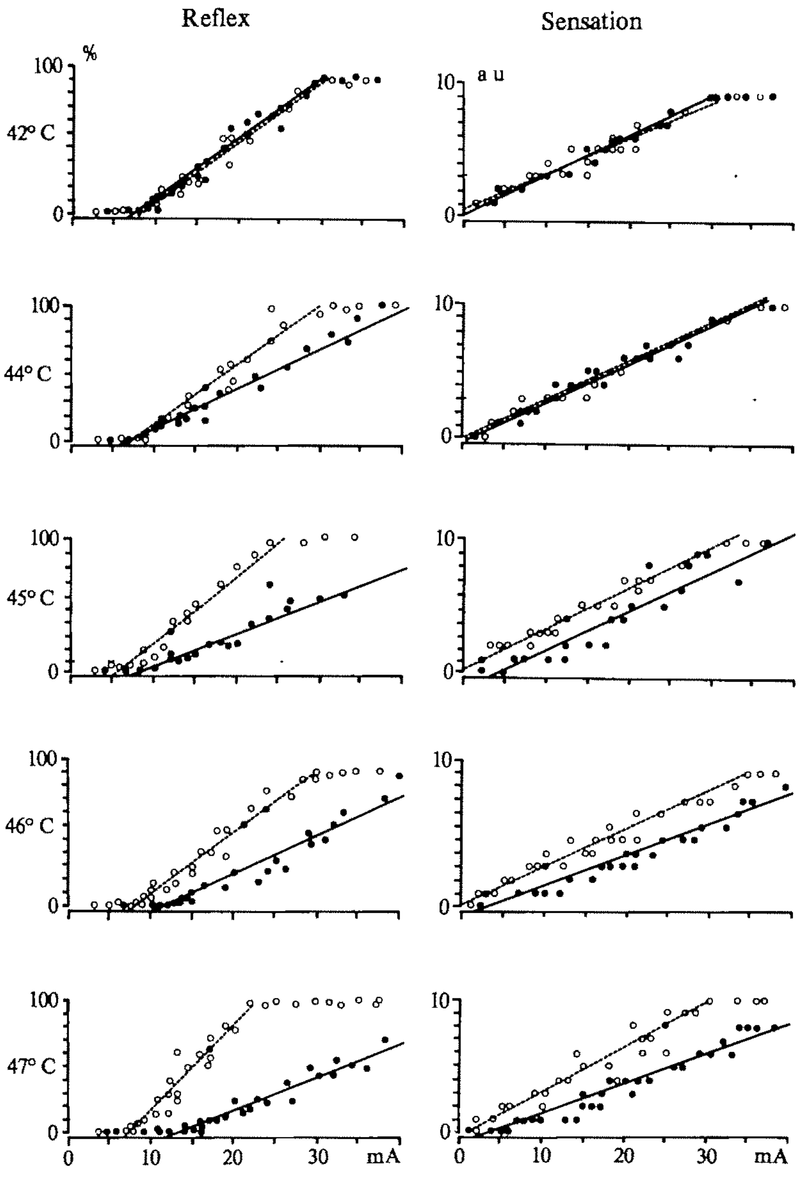

FIG 3. Individual examples obtained in one subject showing the effects of various conditioning thermal stimuli applied to the contralateral hand (temperatures indicated on the left) on the nociceptive reflex activity (*left*) and the corresponding subjective sensation (*right*) induced by sural nerve stimulation (a.u. = arbitrary units). For each sequence, control (open circle, dotted line) and conditioned (filled circle, solid line) recruitment curves are plotted on the same graph (*see text*).

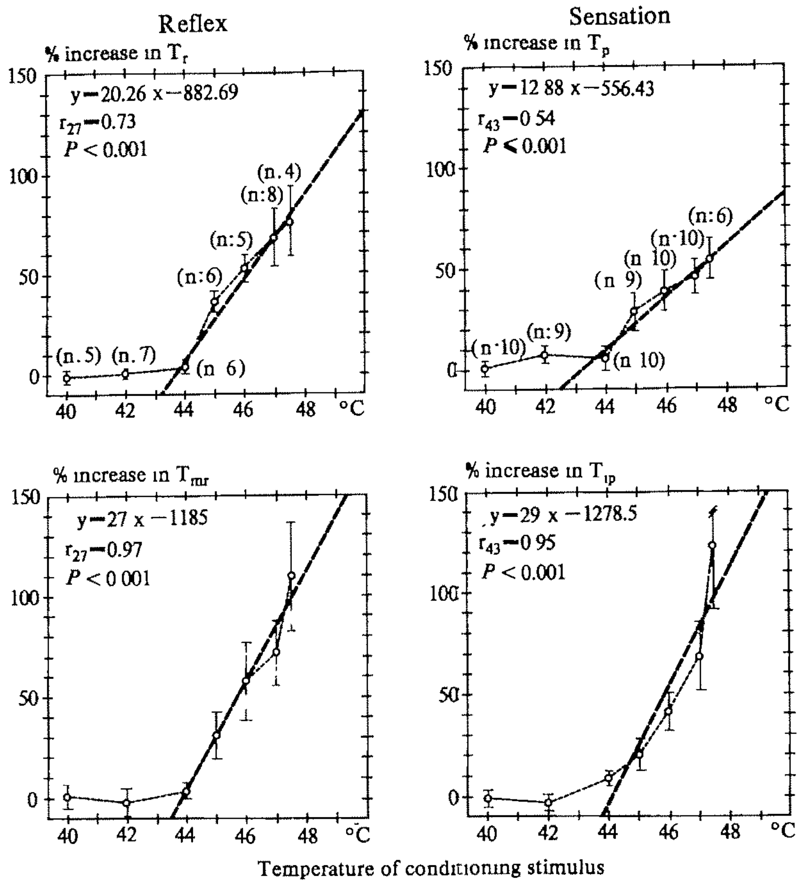

FIG 4. Effects of conditioning thermal (40 to 47.5° C) stimuli applied to the contralateral hand (abscissa) on the four thresholds, as defined in fig 2B (ordinates). Each point indicates the mean (±SEM) percentage increase in threshold (n = no. of subjects). Statistical analysis of regression lines is indicated in the upper left hand corner of each graph.

On considering the curves related to the reflex response (left part of fig. 4), it is seen that the T_r and T_{mr} curves are quite superimposable. From these curves, it can be estimated that the conditioning temperatures which induced a 50 per cent increase in T_r and T_{mr} thresholds were 46.1 and 45.8° C, respectively. On the other hand, by considering the curves related to sensation (right part of fig. 4), it is obvious that the T_p curve is less steep than the one for T_{ip}, the latter resembling those related to the reflex. The estimates of the temperatures which could induce an increase of 50 per cent in T_p and T_{ip} were 47.1 and 45.8° C, respectively. To summarize this section, both the nociceptive reflex and painful sensation evoked by stimulating the sural nerve were similarly affected by heating the contralateral hand in the 44 to 47.5° C range, in a peculiarly close fashion for suprathreshold responses (T_{mr} and T_{ip}).

Effects of Other Conditioning Stimuli

From the results described in the preceding section, it appears that nociceptive flexion reflexes and painful sensations were very significantly depressed by heterotopic heat stimuli in the nociceptive range (*see* Discussion). For further evidence that heterotopic nociceptive stimuli were able to influence both a nociceptive reflex and the related pain sensation, other modalities of noxious conditioning stimuli were tested. The effects of noxious cold, muscular pain and noxious pinch were studied on the four parameters described above.

As shown in fig. 5, which illustrates an individual example, the intensity-reflex and intensity-sensation recruitment curves were substantially shifted to the right by these three conditioning stimuli. The immersion of the contralateral hand into a 6° C waterbath, muscle pain induced by forearm muscular exercise during ischaemia and strong pressure applied to the nasal septum, all resulted in a shift of the curves to

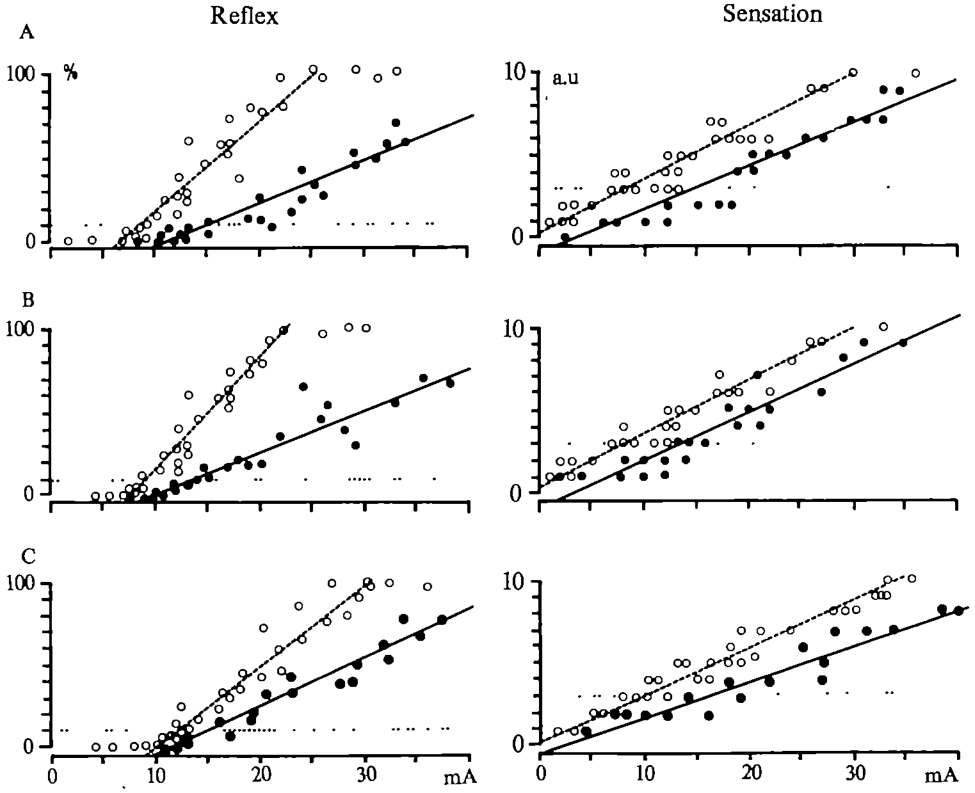

FIG 5 Individual examples obtained in one subject (same as in fig. 3) showing the effects of three heterotopic nociceptive conditioning stimuli (presentation and symbols as in fig 3). A, immersion of the left hand in an agitated waterbath maintained at 6° C. B, 10 watts muscular exercise with the left forearm during an ischaemic block of arterial blood flow achieved using a pneumatic cuff placed around the middle part of the left arm and inflated to 1.5-fold the systolic blood pressure. C, application of a pair of forceps (15 to 20 mm^2; 4.5 kg/cm^2) to the nasal septum

the right, similar to those obtained when the same subject immersed his hand in the 47° C waterbath (*see* lower part of fig. 3).

Data obtained from all the subjects are summarized in fig. 6. Note that the three conditioning stimuli induced a very significant increase in the four thresholds considered in this study (i.e. T_r, T_{mr}, T_p and T_{ip}). The greatest variation observed was induced by the noxious cold applied to the contralateral hand.

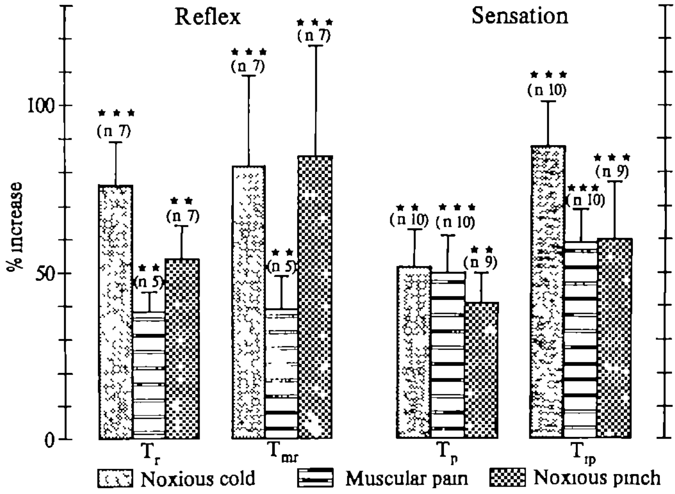

FIG. 6. Effects of three heterotopic nociceptive conditioning stimuli on the four thresholds, as defined in fig. 2B Each column indicates the mean (±SEM) percentage increase in threshold (n = no of subjects; $^{**}P < 0.01$, $^{***}P < 0.001$, paired t test).

Relationships between the Nociceptive Reflex and the Related Painful Sensation during Conditioning Stimulation

In the first paragraph, we have demonstrated that the mean intensity-response recruitment curves were almost identical to the reflex and the sensation. This indicates a close relationship between these parameters in the control situation, as has been described previously (Willer, 1977; Willer *et al.*, 1980). The relationships between the nociceptive reflex and pain sensation during the 10 conditioning situations detailed above will now be considered. In the left part of fig. 7, the mean increases in T_r (abscissa) are plotted against the mean increases in T_p (ordinate) for each conditioning situation; note the linear relationship between the increases of T_r and T_p. On the right of fig. 7 such a relationship can also be observed between the increases of T_{mr} (abscissa) and T_{ip} (ordinate). However, the slopes of these two regression lines are quite different. The slope of the left linear regression line is less steep (tg alpha = 0.63) than a 45 deg line (tg alpha = 1), indicating that T_r was, overall, more sensitive than T_p to the conditioning stimulation. On the other hand,

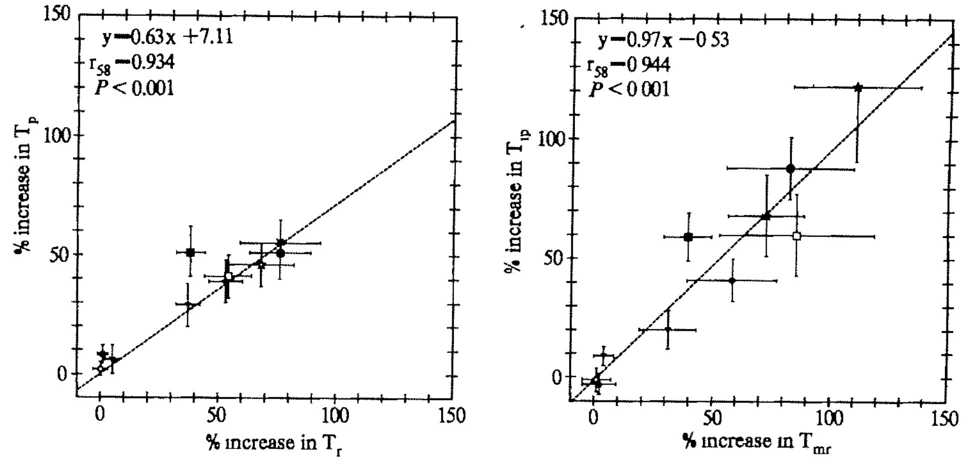

FIG 7. Correlation between the increases in pain and reflex thresholds obtained during all the conditioning stimuli for all subjects Left graph: T_r–T_p relationship; right graph. T_{mr}–T_{1p} relationship. Statistical analysis of regression lines is indicated in the upper left hand corner of each graph. ○· 40° C, ●· 42° C; △. 44° C, ▲: 45° C, ◆· 46° C, ☆ 47° C, ★ 47.5° C, ❁· noxious cold, ■. muscular pain, □: noxious pinch.

an almost 45 deg regression line (tg alpha = 0.97) can be observed on the right of fig. 7, clearly indicating that T_{mr} is, overall, as sensitive as T_{1p} to the conditioning stimuli.

DISCUSSION

The present results demonstrate that experimentally-induced pain can be profoundly modified by nociceptive stimuli applied to heterotopic body areas: pain elicited by electrical stimulation of the sural nerve could be lowered by various nociceptive stimuli applied to the contralateral hand or the nose. In addition, these conditioning nociceptive stimuli were found to depress the simultaneously recorded nociceptive spinal reflex (R_{III}). With regard to the sensation or the reflex, both threshold and suprathreshold responses were similarly affected. These results will be discussed from several points of view. In the first section the methods which we have used for investigating experimentally-induced pain will be considered. In the second we will consider the relevance of our results to the counterirritation phenomena. The involvement of spinal functions in these phenomena will be discussed in a third section, while hypotheses concerning the underlying mechanisms will be considered in the last.

The first question concerns the spinal origin of the nociceptive reflex R_{III}. Although we cannot formally exclude the possibility of the involvement of a spinobulbospinal component in our recordings (*see e.g.*, Shimamura *et al.*, 1964), there is no doubt that this reflex is mainly, if not entirely, organized in the spinal cord since it can be fully observed in paraplegic patients (Hugon, 1973; Willer and Bussel, 1980). The methods used in these investigations followed on from an earlier study (Willer, 1977) in which it was found that there was a close relationship between the threshold of the R_{III} reflex and the threshold of pain elicited by sural nerve stimulation. We have further shown here that the reflex and pain recruitment curves are also closely correlated with suprathreshold stimuli. Of special interest was the observation of a linear relationship for both pain sensation and the reflex response with stimulus intensities over a limited range. As a consequence, the response thresholds (T_r and T_p) and the maximal response thresholds (T_{mr} and T_{ip}) were very similar with the T_{mr}/T_r and T_{ip}/T_p ratios being close to 3 (*see* Table). These findings suggest that, with our experimental conditions the mechanisms for the development of pain, including intolerable levels, have already largely occurred at the periphery and in the spinal cord with few subsequent modifications. We believe that these methods are suitable for pain studies particularly, as discussed below, those related to the modulation of spinal mechanisms.

Our results confirm earlier reports showing that pain thresholds can be increased by a conditioning nociceptive stimulus applied to other areas of the body. Using devices allowing mechanical stimulation of the right and the left forearms, Duncker (1937) reported that the pain sensation induced by the stimulation of one forearm was lowered by the simultaneous nociceptive stimulation of the contralateral forearm in all 40 subjects tested; interestingly, the pressure component elicited by mild stimuli was not affected. Parsons and Goetzl (1945) observed a rise in the threshold to dental pain during the application of a spray of ethyl chloride (nociceptive cold) to the anterior surface of the subject's tibiae. Hardy *et al.* (1940) observed that the progressive pain sensation resulting from ischaemia of the arm was associated with a parallel increase in the threshold for pain elicited by means of thermal radiation of the forehead. More recently, Pertovaara *et al.* (1982) confirmed that pain resulting from ischaemia of the arm associated with muscular exercise strongly increased the dental pain threshold. We have further shown here that suprathreshold pain sensations (T_{ip}) can also be depressed by pain induced by mechanical stimuli, cold or ischaemia. The large reduction in experimental pain observed during the application of nociceptive cold gives experimental support for the use of intense cold for the treatment of clinical pain (Travell, 1952; Grant, 1964; Mennell, 1975; Melzack *et al.*, 1980*b*), such as ice massage of the hand for the relief of dental pain (Melzack *et al.*, 1980*a*).

To our knowledge there are no available data on the use of heat as a conditioning stimulus or on the relationship between the intensity of stimulation and the resultant conditioned pain response. We found here a direct relationship between the conditioning temperature in the nociceptive range (45 to 47.5° C) and the decrease of the conditioned pain sensation. For obvious reasons, higher temperatures were not tested but from fig. 4, it can be presumed that they would readily be effective in lowering pain responses. These observations could explain the efficacy of moxibustion and cautery as drastic pain-relieving methods many years ago.

All these observations are probably relevant to counterirritation phenomena, as defined as the paradoxical pain relieving effect of pain elicited from other regions of the body (*see* Le Bars *et al.*, 1984). In this respect, it is interesting to note that intolerable pain was more sensitive to the counterirritants tested than threshold pain.

Effects of heterotopic nociceptive conditioning stimuli were also found on the R_{III} reflex activity: indeed both T_r and T_{mr} were increased by all conditioning situations. For thermal stimulation, the increase was directly related to the temperature of the waterbath, within the nociceptive range.

The strong relationship between the R_{III} reflex activity and the related pain sensation observed during control responses (*see above*) was also found during the conditioning periods. This was particularly clear for the supramaximal responses to sural nerve stimulation since, when considering all the conditioning situations, the threshold for obtaining a maximal R_{III} reflex and the threshold for intolerable pain were similarly affected (*see* fig. 7, right). It must be noted, however, that the liminal reflex responses were more affected than pain threshold (*see* fig. 7, left). These observations clearly suggest that the inhibitory effects we have described, and most probably the related counterirritation phenomena, would seem to originate mainly from a depression in the transmission of nociceptive messages at spinal level.

The question arises as to whether attentional phenomena related to the conditioning situations could explain our results. Indeed it has been shown that some attentional states can result in a reduction of R_{III} reflexes (Willer *et al.*, 1979) and pain responses (*see* Beecher, 1957). Such a hypothesis seems unlikely in our experimental situation for the following reasons. The immersion of the right hand in a 40, 42 or 44° C waterbath had no effect on the parameters studied (*see* fig. 4). In addition, in a pilot study (unpublished data), we found that the muscular exercise used in the present work was without effect in the absence of ischaemia. Finally, a mental calculation test was also without effect on the R_{III} reflex. Thus it can be concluded that the observed inhibitory effects were not due to the experimental situation but rather to the nociceptive nature (*see below*) of the conditioning stimuli.

It might be argued that the nociceptive nature of the conditioning stimuli could have induced a state of stress, which in turn could be responsible for the inhibitory effects. Indeed various stressful factors have been shown in animal studies to induce a rise in the threshold of nociceptive reactions ('stress-induced analgesia', *see* references in Tricklebank and Curzon, 1984). In man, a progressive increase in R_{III} reflex threshold takes place when a repeated anxiety-provoking situation occurs, as from anticipation of a severe pain (Willer *et al.*, 1981). This increase requires at least 30 min to become significant. By contrast, in the present study, the inhibitory effects were observed as soon as the conditioning stimuli were applied; furthermore we have no evidence for an increased efficacy of the conditioning stimuli over the 2 to 3 min test period. In addition, we have deliberately excluded intolerable conditioning stimuli (e.g. $> 47.5°$ C) for which stressful reactions would be obvious. Finally, with a paradigm similar to one of those we have used, Pertovaara *et al.* (1982) reported that the pain resulting from 15 min ischaemia associated with controlled muscular exercise of the arm did not change the ACTH plasma concentration. Therefore, while we cannot formally exclude stress factors, it seems likely that they played a minor role, if any, in the inhibitory effects observed.

It is worth pointing out the contrast between (1) the phasic nature of the conditioned stimulus (20 ms electrical train) and the long duration (2 to 3 min) of the nociceptive conditioning stimuli; (2) the relatively restricted central input (part of S1) of the sural nerve compared with the wide distribution of the central input evoked by our conditioning stimuli; and (3) the larger central somatotopic representation of the hand and the nose compared with that of the foot. There was therefore a clear imbalance between the afferent volleys triggered by the conditioning and the conditioned stimuli. Previous studies (Willer *et al.*, 1978) have shown that the stimulation parameters used in the present work for eliciting a R_{III} reflex activate predominantly the myelinated fibres of the peripheral nerve. The nociceptive conditioning stimuli we have used, most probably involved Aδ and C fibre nociceptive afferents. This seems particularly clear for thermal conditioning stimuli since 40 to 44° C were ineffective whereas inhibitory effects were found for 45 to 47.5° C in a direct relationship with these temperatures (*see* fig. 4). In man, the pain threshold for thermal stimulation is achieved when skin temperature reaches approximately 45° C (Hardy *et al.*, 1951) and pain scaling is possible only in the 44 to 50° C range (Adair *et al.*, 1968; LaMotte and Campbell, 1978). In addition, pain scaling has been shown to be correlated with the firing of polymodal nociceptors during thermal noxious stimulation (Gybels *et al.*, 1979; Adriaensen *et al.*, 1983). Taken together, these data suggest that the observed inhibition induced by heterotopic thermal conditioning stimuli parallel both the pain sensation and the response of peripheral nociceptors.

In summary, our data show that, whether induced by heat, cold, mechanical or chemical procedures, a painful conditioning stimulus strongly depresses, at spinal level, the nociceptive messages elicited from remote localized body areas. The site of application of the effective conditioning nociceptive stimuli could be far from the site of origin of the conditioned pain response, thus excluding segmental mechanisms and the involvement of trigger points (Travell and Rinzler, 1952).

The close relationship between the effects of the conditioning stimuli on the reflex and the related sensation argues against a mechanism of inhibition acting on the motoneuronal pool. Instead, such a relationship suggests that these inhibitory mechanisms modulate a common spinal interneuronal pool responsible for both nociceptive reflex and ascending pain pathways. The question arises as to the identity of the pathways mediating such inhibitory mechanisms and, more particularly, whether they are confined to the spinal cord or whether they extend to supraspinal structures.

If intraspinal pathways are postulated, very long pathways must be implicated since the responses elicited by stimulation of the sural nerve (S1 dermatome) could be modified by conditioning stimuli applied on the hand (D1 to C6 dermatomes) or on the nose (trigeminal area). Anatomical studies in animals (*see* Cadden *et al.*,

1983) and in man (*see* Nathan and Smith, 1959) have revealed the existence of propriospinal pathways which might be able to mediate remote effects of nociceptive stimuli. In the spinal cat, the flexor reflex of the hindlimb can be inhibited by contralateral nerve stimulation (Eccles and Sherrington, 1931) and forelimb polysynaptic reflexes can be inhibited by nociceptive stimulation of the hindlimb (Miller *et al.*, 1973). In addition, there is evidence in both rat (Fitzgerald, 1982; Cadden *et al.*, 1983) and monkey (Gerhart *et al.*, 1981) that some dorsal horn neurons involved in the transmission of nociceptive information can be inhibited by heterotopic nociceptive stimuli *via* a propriospinal mechanism. However, these inhibitions appear to be relatively weak, to adapt rapidly and to be more marked for conditioning stimuli applied to structures proximal to the excitatory receptive field of the neurons under study than for stimuli applied more distally (Cadden *et al.*, 1983). In any case, if these mechanisms might partly explain our results obtained by conditioning the hand, they do not explain the inhibitions triggered from the nose.

The observations reported in the present study seem more relevant to the 'diffuse noxious inhibitory controls' (DNIC) which have recently been described in the rat (Le Bars *et al.*, 1979*a*, 1982). These controls affect dorsal horn convergent neurons and most of their features can be observed during recordings from neurons driven from receptive fields located on the hindpaw. The following points appear common with the inhibitions described above. (1) The responses of convergent neurons to electrical stimulation of their receptive fields can be inhibited by various noxious stimuli applied to parts of the body distant from the excitatory receptive field, including trigeminal areas (e.g. pinching the nose). (2) The distance between conditioned and conditioning sites of stimulation is not a critical factor for the strength of inhibition. (3) All types of conditioning nociceptive stimuli, whether mechanical, thermal or chemical, are effective. (4) The conditioning stimulus requires spatial and temporal summation much greater than the duration and strength of the conditioned stimulus to be fully effective. (5) In these conditions the inhibitory effects are very powerful, affecting responses to both threshold and suprathreshold electrical shocks. (6) DNIC are directly related to the strength of conditioning stimulation. Of special interest are the observations on DNIC triggered by heat conditioning stimuli: the threshold for obtaining an inhibitory effect was found between 40 and 44° C and, above this, a very significant correlation was observed between the conditioning temperature and the degree of inhibition (Le Bars *et al.*, 1981). (7) Finally, DNIC have been shown to affect both the responses of spinothalamic convergent neurons (Dickenson and Le Bars, 1983) and the polysynaptic reflex discharges evoked in the common peroneal nerve following electrical stimulation of the sural nerve (Schouenborg and Dickenson, 1984). These observations indicate the ability of DNIC to modulate nociceptive information transmitted by ascending pain pathways and also by nociceptive reflex pathways.

These parallels lead us to believe that the inhibitory effects observed here in man and DNIC in the rat share common mechanisms. Since DNIC has been shown to be sustained by a complex loop ascending from and redescending to the spinal cord

(Le Bars *et al.*, 1979*b*), further investigations are needed to substantiate our hypothesis. It will be crucial to know whether the type of inhibitory effects reported here can be observed in patients with paraplegia following complete spinal cord transection. If they are absent, our experimental approach would then seem to be appropriate for the further investigation in man of descending inhibitory controls triggered by nociceptive inputs.

ACKNOWLEDGEMENTS

We wish to thank Miss M. Cayla for assistance in the preparation of the manuscript and Drs J. M. Besson, S. W. Cadden and P. W. Nathan for helpful advice. This work was supported by l'Institut National de la Santé et de la Recherche Médicale (INSERM), CRL No. 826029.

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(*Received January 24, 1984. Revised April 24, 1984*)

Brain (1984), 107, 1113-1122

DEGRADED DISCRIMINATION BETWEEN SPEECH-LIKE SOUNDS BY PATIENTS WITH MULTIPLE SCLEROSIS AND FRIEDREICH'S ATAXIA

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SUMMARY

We previously found that some patients with multiple sclerosis are selectively 'deaf' to changes in the pitch of a tone, even when audiometric sensitivity to pure tones is unimpaired. This subtle form of deafness is not experienced by patients with noise-induced hearing loss of exclusively peripheral origin. It was suggested that this auditory defect may be one possible cause for difficulties in discriminating speech, on the grounds that frequency changes in the speech waveform are known to be important for intelligibility. This implication is not self-evident; our earlier studies tested hearing with a single pure tone that was either frequency-modulated or amplitude-modulated, while even a simple approximation to speech sounds involves not one, but three narrow bands of noise (formants) whose frequencies and intensities change from instant to instant.

The present study has investigated the ability of subjects to discriminate between speech-like sounds. These consisted of three formant frequencies generated by computer. The only difference between the sounds was that the lowest-frequency formant rose or fell in pitch by different amounts. In order to ensure that subjects used frequency (pitch) cues rather than any associated loudness cues we mixed different loudness shifts with the frequency shifts. Nineteen control subjects, 25 patients with multiple sclerosis (MS) and 4 patients with Friedreich's ataxia (FA) were tested. Nine of the patients with MS and all 4 patients with FA gave results that fell outside the range of the control subjects. A possible pathophysiological basis for this observation is the finding that some neurons in the auditory pathway of animals respond preferentially to changes in tone frequency: homologues of these neurons might be functionally impaired in some patients with MS and FA.

INTRODUCTION

We previously reported that some patients with multiple sclerosis are specifically 'deaf' to changes in tone pitch even when auditory sensitivity to pure tones is not impaired. This subtle form of deafness was not observed in patients with noise-induced hearing loss, whose disorder was presumably restricted to peripheral auditory structures (Quine *et al.*, 1984). Frequency-shift deafness can be understood in terms of the concept that the auditory pathway contains separate neural mechanisms sensitive to changes in the intensity and pitch of a tone (Kay and Matthews, 1972; Nábêlek, 1978; Gardner and Wilson, 1979; Regan and Tansley, 1979; Tansley and Regan, 1979; Cullen and Collins, 1982).

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It has been suggested that patients with degraded ability to hear changes in tone pitch might, as a result, have speech comprehension problems and that this could be one reason why some patients with normal audiograms score poorly on speech tests (Tansley and Regan, 1979). The idea behind this suggestion is that frequency changes in the speech waveform are known to be important for speech intelligibility (Delattre *et al.*, 1955; Lehiste and Peterson, 1961). The present study, in which we measured the ability of subjects to discriminate between speech-like sounds, tests this suggestion.

METHODS

Test Stimuli

In order to have close control over the test stimuli we used computer-generated speech sounds rather than natural speech. Sounds were synthesized on the parallel speech synthesizer at the Haskins Laboratory, New Haven, Connecticut. It generated a fundamental frequency with a rich harmonic structure which was then passed through three parallel filters to produce three formant frequencies much like human speech. Each sound that we synthesized had a nominal fundamental frequency of 72 Hz, a duration of 400 ms, and a 40 ms rise and fall time. The first formant frequency (i.e. centre frequency of the first formant filter) was nominally 500 Hz, the second was set to a nominal value of 1535 Hz and the third to a nominal value of 3029 Hz for all tests in this study. Several discrete frequency and intensity shifts were generated for the first formant; discrimination between these different sounds provided the basis for this study. Discrimination losses detected by this procedure may not be evident

TABLE 1. CHANGE IN THE FREQUENCY AND INTENSITY OF THE FIRST FORMANT FOR EACH OF THE 15 SPEECH-LIKE SOUND STIMULI

Stimulus	*Frequency shift* (*Hz*)	*Intensity shift* (*dB*)
F400	714–304	0
F200	611–407	0
F100	560–458	0
F 50	535–483	0
R 50	483–535	0
R100	458–560	0
R200	407–611	0
R400	304–714	0
L −9	0	−6 to +3
L −6	0	−3 to +3
L −3	0	−3 to 0
L 0	0	0
L 3	0	+3 to 0
L 6	0	+3 to −3
L 9	0	+6 to −3

in everyday life since there is considerable redundancy in normal speech. The initial and final values for the frequency and intensity of the first formant for each of the 15 different stimuli used are listed in Table 1. Fig. 1 shows sonograms of the stimuli listed as R400, R200, L0, F200, and F400. The meaning of these labels is brought out in the figure; for example, the frequency of the first formant rose by 400 Hz during the R400 stimulus, was constant during the L0 stimulus and fell 400 Hz during the F400 stimulus.

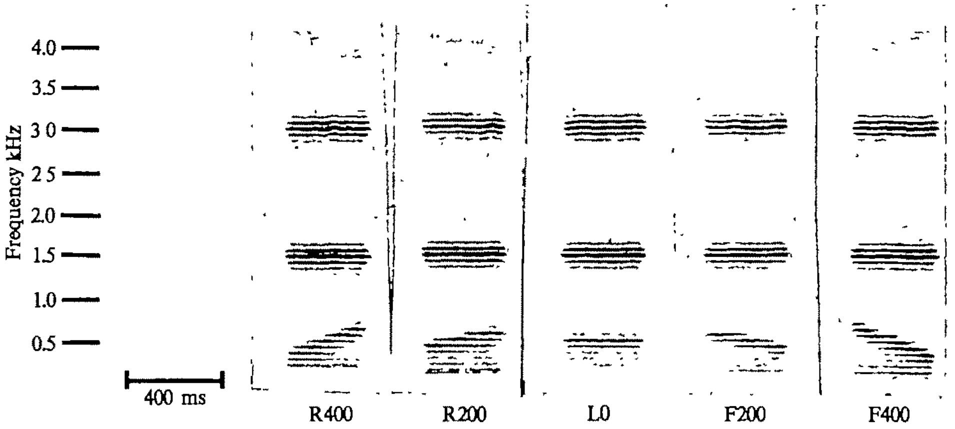

FIG. 1. Sonograms of five speech-like sound stimuli illustrating the first, second and third formants. For stimulus R400, the pitch of the first formant rises by 400 Hz during the 400 ms stimulus duration. For stimulus R200, the pitch of the first formant rises 200 Hz, for L0 it is constant, for F200 it falls 200 Hz and for F400 it falls 400 Hz. Intensity changes are not shown.

Experiment 1. In Experiment 1 we measured the minimum frequency shifts of the first formant that subjects could detect. Three tape-recorded sounds were presented to the subject in each trial. Two of the sounds were identical and the third ('target') sound differed from the other two. The subject's task was to indicate which of the three sounds was different from the other two by pressing one of three buttons labelled 1, 2 and 3. The target sound was presented in each position (first, second or third) three times; there were a total of 9 trials with each of the nine target sounds for a total of 81 tests in a session. The test sequences were presented in a random order. Stimuli F400, F200, F100, F50, L0, R50, R100, R200, R400 were the target sounds while L0 was always used for the two identical sounds. Discrimination among three L0 stimuli provided a control test condition; performance fell quite close to the predicted 33 per cent resulting from random guesses among three alternatives.

Test tapes were played on an Otari MX 5050B 2HD two-track tape recorder at 7.5 ips. The tapes were started and stopped under remote control by a 32K microcomputer (PET 2032). The subject sat in a soundproof chamber and was stimulated monaurally through Stax SRX Mk. 3 headphones. The button-press responses made by the subject were recorded directly by the microcomputer which controlled the experiment. Individual differences in a subject's audiometric thresholds were allowed for by setting stimuli at a fixed amount (50 dB) above the subject's individual threshold (i.e. at 50 dB SL). Subjects were given at least 10 practice trials before the test session began and those few subjects who had difficulty were given additional trials with easier stimuli until they consistently responded correctly. Each test sequence lasted about 5.2 s; there was 1 s of silence before and after each of the three stimuli. The subject was allowed as long as necessary to respond before the next sequence commenced. Visual feedback was provided to inform the subjects when they responded correctly. Informed consent was obtained after the procedure had been explained.

Experiment 2. The second experiment was designed to distinguish between frequency cues and intensity cues in discriminating between speech-like sounds. As in Experiment 1, three tape-recorded sounds, two of which were identical, were presented to the subject. The target sound was either F200 or R200; both of these sounds were easily discriminated from L0 by control subjects. The target was presented in each position (first, second or third) three times. The two identical sounds were either L−9, L−6, L−3, L0, L3, L6 or L9. Thus the nontarget sounds were always of constant frequency but the intensity of the first formant might rise, remain level, or fall during the 400 ms duration of the sound. There was a total of 9 trials with each of the eight identical pairs for a total of 72 tests in a session. The test sequences were presented in a random order. A control sequence was included in which all three stimuli were the target sound. This discrimination of the target sound from two target stimuli provided a test condition that controlled against artifactual cues; performance fell quite close to the predicted 33 per cent correct resulting from random guesses among three alternatives. Informed consent was obtained after the procedure had been explained.

PATIENTS AND CONTROLS

Tests were conducted on three groups of subjects: 19 control subjects aged 16 to 61 years, 25 patients with multiple sclerosis (MS) aged 19 to 62 years, and 4 patients with Friedreich's ataxia (FA) aged 15 to 38 years. The diagnostic criteria for MS were those set out by Schumacher *et al.* (1965) according to the scheme described by Rose *et al.* (1976). The auditory pathway is known to be affected in MS (Noffsinger *et al.*, 1972; Robinson and Rudge, 1975, 1977; Grénman and Salmivalli, 1982). Cortical as well as peripheral auditory involvement has been reported in FA although this was not common (3 of 12 patients) (Taylor *et al.*, 1982). Audiograms were measured with a Grason-Stadler model 1704 audiometer. Hearing losses are shown in Tables 3 to 5. Of 25 patients with MS, 21 had no clinical loss (a clinical loss is 20 dB or more). Of 4 patients with FA, 3 patients had a clinical loss. (Note that sound intensities were corrected for each subject's individual threshold.)

RESULTS

Experiment 1. Threshold Frequency Shift

Fig. 2 shows the percentage correct responses for the nine different speech-like sounds averaged over the 19 control subjects. Numerical data are given in

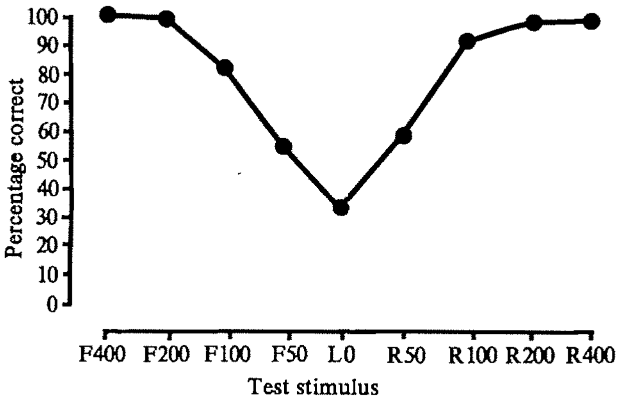

FIG. 2. Percentage correct identification of different frequency shifts by control subjects.

Tables 2 and 3. L0 means that the target sound was the same as the two comparison sounds, that is, all three sounds in any trial had no frequency shift and no intensity shift. Fig. 2 shows that the percentage correct responses approximated to the 33 per cent that would be given by random guesses. Table 3 shows little relation between audiometric threshold and performance on our test (compare subjects 8, 9, 12 and 15).

TABLE 2 PERCENTAGE DISCRIMINATION FOR CONTROL SUBJECTS BETWEEN THE CONSTANT-FREQUENCY (L0) STIMULUS AND THE 9 SPEECH-LIKE STIMULI SHOWN IN THE LEFT COLUMN

Stimulus	*Mean percentage correct*	*SD (%)*
F400	100	0.74
F200	97	7.7
F100	80	16
F 50	55	18
L 0	34	8.7
R 50	58	10
R100	91	9.0
R200	99	2.5
R400	99	1.9

Mean data and standard deviations are shown for 19 subjects (29 ears). Variability is given in terms of standard deviations, although the distributions were somewhat asymmetric. Stimulus intensities were adjusted to take account of individual audiometric thresholds. Key to column 1 is given in Table 1.

Overall, the MS patients had poorer discrimination than controls for all test sounds. Table 4 sets out individual data for the 25 MS patients and Table 5 individual data for the 4 FA patients. Comparison by Student's t test for controls *vs* MS patients was as follows: for F400 $P < 0.005$, F200 $P < 0.005$, F100 $P < 0.0005$, R100 $P < 0.0005$, R200 $P < 0.05$, and for R400 $P < 0.1$. As for control subjects, there was little relation between audiometric threshold and performance on our test (compare patients 4, 12 and 24).

Experiment 2. Titration with Intensity

In Experiment 2 we examined more carefully the intensity sweep in each sequence for which the subject had the most difficulty in discriminating from the target frequency sweep. We added different amounts of intensity change to this frequency sweep so as to cancel any intensity cues and thus force subjects to use frequency sweep cues only. In the F200 test, controls had an average of 93 per cent (SD = 8.8) correct on the tests while the patients with MS and FA had an average of 73 per cent (SD = 22) and 51 per cent (SD = 28) correct, respectively. In the R200 test, controls

TABLE 3 PERCENTAGE CORRECT DISCRIMINATION BY CONTROL SUBJECTS BETWEEN F200 AND L0 STIMULI AND BETWEEN R200 AND L0 STIMULI

Subject No.	*Age (yrs)*	*Ear*	*Percentage correct discrimination*		*Hearing loss (dB)*
			F200	*R200*	
1	58	L	94	94	5
2	61	L	100	100	5
2	61	R	100	100	10
3	42	L	94	100	10
3	42	R	96	100	5
4	38	L	100	100	5
4	38	L	100	100	5
5	28	L	100	100	5
6	20	L	88	94	5
6	20	R	88	83	5
7	19	L	88	88	5
7	19	R	88	94	10
8	16	R	100	100	35
9	58	L	88	94	10
9	58	R	66	94	10
10	59	L	88	100	25
10	59	R	88	81	20
11	31	L	100	94	5
11	31	R	94	94	5
12	27	L	94	94	0
12	27	R	100	100	0
13	46	L	100		10
14	43	R	94	88	10
15	24	L	72	66	5
15	24	R	77	66	5
16	20	L	100	100	5
16	20	R	100		5
17	40	L	88	94	0
18	20	L	94	94	10
19	18	L	100	100	5

Data shown are for 30 ears of 19 individual subjects. Stimulus intensities were adjusted to take account of individual audiometric thresholds. Key to stimuli is given in Table 1.

had an average of 93 per cent (SD = 9.3) correct on the tests while the patients with MS and FA had an average of 83 per cent (SD = 18) and 44 per cent (SD = 18) correct, respectively. All the control subjects achieved the criterion level of 66 per cent correct (3 SD worse than the control mean) on both F200 and R200 while 9 (36%) patients with MS and all 4 patients with FA could not achieve the criterion level in one or more intensity conditions. Overall, patients with MS had more

TABLE 4 PERCENTAGE CORRECT DISCRIMINATION BY MS PATIENTS BETWEEN F200 AND L0 STIMULI AND BETWEEN R200 AND L0 STIMULI

Patient No.	*Age (yrs)*	*Ear*	*Percentage correct discrimination*		*Hearing loss (dB)*
			F200	*R200*	
1	34	L	88	77	5
2	34	L	44	88	10
3	53	L	85	88	10
3	53	R	81	81	15
4	38	L		88	10
4	38	R		55	10
5	43	R	33		15
6	42	L	83	88	10
6	42	R	72	84	10
7	36	L	88	88	5
7	36	R	88	83	5
8	39	L	44	88	20
9	38	L	88	88	10
9	38	R	88	88	10
10	57	L	66	66	15
11	34	L	59	83	5
11	34	R	55	94	10
12	28	R	66		5
13	50	L	88	94	10
13	50	R	88	88	10
14	30	L	40	88	20
14	30	R	63	88	20
15		L	33	33	10
15		R	33	33	10
16	19	L	88	100	0
16	19	R	88		5
17	23	L	88	100	10
17	23	R	77	88	10
18	53	L	88	94	10
18	53	R	88	88	10
19	54	L	94	100	0
19	54	R	94	100	−5
20	62	L	88	88	20
20	62	R	100	77	10
21	40	L	77		5
21	40	R	55	100	5
22	29	L	11	22	15
23	32	L	83	100	10
23	32	R	88	88	5
24	46	L	100	88	25
24	46	R	84	88	25
25	61	L	66	88	5

Data shown are for 42 ears of 25 individual patients. Stimulus intensities were adjusted to take account of individual audiometric thresholds. Key to stimuli is given in Table 1.

TABLE 5. PERCENTAGE CORRECT DISCRIMINATION BY FA PATIENTS BETWEEN F200 AND LO STIMULI AND BETWEEN R200 AND LO STIMULI

Patient No.	*Age (yrs)*	*Ear*	*Percentage correct discrimination* *F200*	*R200*	*Hearing loss (dB)*
1	15	L	94	77	10
1	15	R	77	55	10
2	38	R	33	33	70
3	35	L	33	33	35
3	35	R	33	33	25
4	19	L	33	33	30

Data shown are for 6 ears of 4 individual patients. Stimulus intensities were adjusted to take account of individual audiometric thresholds. Key to stimuli is given in Table 1.

difficulty with the F200 discrimination (U test, $p < 0.00003$) and the R200 discrimination (U test, $P < 0.0002$) than did the control subjects. Likewise, the patients with FA had more difficulty with the F200 discrimination (U test, $P < 0.0007$) and with the R200 discrimination (U test, $P < 0.0001$) than did the control subjects.

DISCUSSION

The test stimulus used in our previous study was a simple tone whose frequency shifted upwards or downwards. Speech sounds are much more complex. However, some speech sounds can be approximated by three narrow bands of noise (formants) whose frequencies and intensities change from instant to instant. It is not self-evident that conclusions about human hearing based on responses to simple tones will be valid for complex speech sounds. We report here an experimental test that the concept of selective 'deafness' to shifts in the pitch of an isolated tone can help to explain confusions between speech-like sounds whose auditory spectrum is much more complex than a simple tone.

Experiment 1 was a screening test to find the largest shift in formant frequency that was confused with a fixed-frequency formant. It is possible, however, that some subjects detected, not the frequency shift, but loudness changes associated with the change in formant frequency. Therefore in Experiment 2, subjects were required to discriminate between shifts of formant frequency in the presence of shifts of formant intensity: in effect, we 'titrated off' loudness changes associated with frequency shifts (Tansley *et al.*, 1982). In Experiment 2 we envisaged that any subject who was using intensity rather than frequency cues to discriminate the speech-like sounds would fail to discriminate between some unique balance of intensity shift and frequency shift. For control subjects we were unable to find an intensity shift that prevented any subject from discriminating between a fixed formant frequency and a 200 Hz shift. We therefore concluded that control subjects were all able to use a 200 Hz frequency cue. Some patients gave results completely outside this control range: 9 of the MS patients tested and all the FA patients were unable to discriminate a 200 Hz formant frequency shift from some of the intensity shifts. Three of the FA patients performed even worse: they could not discriminate the 200 Hz formant frequency shifts from any of the intensity sweeps and two could not even discriminate the 400 Hz frequency sweeps from any of the intensity sweeps. This implies that 9 of the 25 patients with MS and all 4 patients with FA were unable to use frequency cues to discriminate speech-like sounds that control subjects and some patients with MS could discriminate on the basis of frequency cues alone.

Although there is evidence that auditory signals can be desynchronized in patients with MS (Quine *et al.*, 1983), this does not explain a differential loss for increasing *vs* decreasing pitch (e.g. patients 2, 8, 11, 14 and 21 in Table 4; *see also* Quine *et al.*, 1984).

Our finding is consistent with evidence (Quine *et al.*, 1984) that some patients with MS experience a selective impairment of sensitivity to changes in the pitch of a tone. A possible pathophysiological basis for these observations is the finding that some neurons in the auditory pathway respond preferentially to changes in the pitch of a stimulus tone (Whitfield and Evans, 1965; Erulkar *et al.*, 1968): homologues of these neurons might be functionally impaired in some patients with MS and FA.

ACKNOWLEDGEMENTS

Dr A. Liberman allowed us to use the Haskins Laboratory Parallel Speech Synthesizer and Terry Halwes aided us in the synthesis of the sounds used in this study. Dr B. R. Moore provided the sonograms. Pauline Weldon of the Multiple Sclerosis Research Centre at Dalhousie University assisted in finding patients. D.B.Q. was supported by a grant from the Multiple Sclerosis Society of Canada. Grant HD-01994 from the National Institute of Child Health and Human Development to the Haskins Laboratory supported our use of the computer facilities.

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(*Received July 27, 1983. Revised April 24, 1984*)

Brain (1984), **107**, 1123-1142

NEURO-OTOLOGICAL MANIFESTATIONS OF MIGRAINE

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SUMMARY

Vestibulocochlear derangements have been studied in three groups of patients: 200 unselected patients with migraine (Series I), 80 migrainous patients referred because of their symptoms for full neuro-otological examination (Series II), and 116 patients with tension headache who served as controls (Series III). Significant differences were established between tension headache and migraine in respect of incidence and severity of symptoms and their time of onset in relation to the headache. In migraine, vestibulocochlear disturbances can occur as an aura, accompanying the headache or during headache-free periods, the highest incidence occurring during the headache. In Series I, 59 per cent reported vestibular and/or cochlear symptoms and these were of disabling severity in 5 per cent. Significantly, 50 per cent had a history of motion sickness and 81 per cent experienced phonophobia during the headache, the probable mechanism of which is discussed.

Persisting vestibulocochlear derangements were found in 77.5 per cent of Series II, largely vestibular and of both central and peripheral origin. Involvement of the vertebrobasilar vascular system appears to be the most likely explanation. Possible links between Ménière's disease, benign paroxysmal vertigo and migraine are discussed.

INTRODUCTION

The association of disorders of hearing and balance with migraine has long been recognized. As early as AD 131 Aretaeus of Cappadocia (cited in Sachs, 1970) gave a particularly colourful description of the occurrence of both during what was undoubtedly an attack of migraine. In more modern times, it was Liveing in 1873 who was the first to draw attention to the clear association of vertigo with migraine. Since then, Gowers (1907), Symonds (1926) and Graham (1968), amongst others, have all taken the view that vertigo and/or disturbance of hearing can truly be described as migrainous prodromata. In particular, Bickerstaff (1961) introduced the concept of 'basilar artery migraine', that is, attacks of migraine commencing with visual disturbances, vertigo, ataxia, slurred speech, tinnitus and sensory disturbances of the distal parts of the limbs and around the lips followed by throbbing, occipital headache.

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Disturbances of hearing and balance of various kinds have also been reported to occur during the headache phase of the attack (Boenheim, 1917; Heveroch, 1925; Symonds, 1926; Richter, 1935; Heyck, 1958; Wolff, 1963), while the suggestion that vestibulocochlear disturbances can be considered as migraine equivalents, that is, recurrent attacks without ensuing headache, has also been advanced (Heveroch, 1925; Symonds, 1926; Richter, 1935; Levy and O'Leary, 1947; Graham, 1968; Friedman, 1969; Fedorova, 1970). Permanent sequelae such as retinal ischaemia, oculomotor palsies, hemiparesis, facial palsy, and derangement of the eighth nerve system, following repeated attacks of migraine, have also been recognized.

Prominent amongst disturbances of hearing is the phenomenon of phonophobia or intolerance of loud noise which, as vividly described by Tissot in 1778 (cited in Sachs, 1970) can at times match the distress caused by the headache. Interestingly there appears to be a particular susceptibility of motion sickness sufferers to develop migraine (Symonds, 1926; Childs and Sweetnam, 1961; Fedorova, 1970; Pearce, 1971; Kuritzky *et al.*, 1981*b*), while several other authors have commented upon a possible relationship between migraine and Ménière's disease (Atkinson, 1943, 1944; Golding-Wood, 1960; Hinchcliffe, 1967*a*, *b*; Fedorova, 1970), including Ménière himself (cited in Harrison and Naftalin, 1968). Even positional paroxysmal vertigo has been implicated (Schiller and Hedberg, 1960). Nevertheless the pathogenesis of vestibulocochlear signs and symptoms in migraine remains a matter of some speculation.

Although formerly, paroxysmal unilateral headache, associated with nausea and/or vomiting, and disturbances of cerebral function were accepted as diagnostic criteria of migraine, in the last few decades the term has also been used more widely to include recurrent bilateral headaches of vascular type associated with nausea and photophobia with or without accompanying neurological symptoms. Attacks with prodromata consisting of visual, sensory or motor disturbances or in association with these disturbances are designated 'classical' and those without, 'non-classical' or common migraine (Ad Hoc Committee on Classification of Headache, 1962). Although it has been customary in defining classical migraine to restrict consideration to focal cerebral and retinal disturbances it would seem highly likely that similar mechanisms are involved in brainstem, cerebellar and labyrinthine disturbances such as dysarthria, ataxia, loss of consciousness, vertigo and hearing disorders, since all affected structures receive their vascular supply from the vertebrobasilar system. It has to be admitted, however, that difficulties in differential diagnosis clearly arise when these are the only neurological symptoms preceding or accompanying the attacks of headache. For this reason the investigation to be described has been concerned with the prevalence and significance of vestibulocochlear disturbances in migraine, their character and temporal relationship to the attacks of headache and the persisting neuro-otological derangements which have been encountered.

MATERIAL AND METHODS

Two series of patients were selected for study. Series I consisted of 200 unselected migraine sufferers taken in sequence from the City Migraine Clinic and Headache Outpatient Clinic of the National Hospital, Queen Square; 58 males and 142 females were interviewed by one of us (A.K.) in order to ascertain the prevalence and character of their vestibulocochlear symptoms. Their ages ranged from 12 to 74 years with an average age of 42 years. A questionnaire was designed, aimed at obtaining a detailed description of vestibulocochlear symptoms if present, their relation to the time of attacks of migraine and to head and body posture, their frequency, time of onset and relationship to the site of headache. The patients were also questioned about any previous history of ear disease and attention given to any past or recent history of motion sickness. The features of the migrainous attacks characteristic of each individual patient were also noted.

In addition, by way of a control group, the same questionnaire was administered to 116 patients, 72 females and 44 males with tension headache, likewise taken in sequence from the City Migraine Clinic and the National Hospital Headache Outpatient Clinic (Series III). Their ages varied between 17 and 78 years with an average age of 40 years. Series II consisted originally of 207 migrainous patients referred because of disturbances of hearing or balance or both to the Medical Research Council Neuro-otology Unit at the National Hospital from 1943 to the end of 1971 upon whom full neuro-otological examination had been undertaken. Of these, 127 were eliminated on the grounds that either the diagnosis of migraine was in doubt or there was evidence of some other disease. Evaluation was carried out on the remaining 80 cases—30 males and 50 females, aged between 14 and 67 years with an average of 39 years. The investigations included tests of stance and gait with eyes open and closed, examination of eye movements for exclusion of spontaneous nystagmus, tests of optokinetic and positional nystagmus, caloric tests (Fitzgerald and Hallpike, 1942) and pure tone audiometry including air and bone conduction. Electronystagmography, rotational tests, and other audiometric tests were also applied as necessary (Cawthorne *et al.*, 1969; Hood, 1969).

For comparison, the clinical records of 500 patients with multiple sclerosis who had been investigated neuro-otologically were reviewed, and the incidence of Ménière's disease and benign positional vertigo noted. Strict criteria were adopted for the diagnosis of Ménière's disease and benign paroxysmal vertigo following the description given by Dix and Hallpike (1952).

RESULTS

Migraine and Tension Headache

Neuro-otological symptoms. Of the 200 migrainous patients of Series I, 118 reported vestibulocochlear symptoms of one kind or another (59%), in contrast to 35 of the 116 patients with tension headache (30.2%). This difference was significant (χ^2 test, $P < 0.001$). Of the Series I migrainous patients, 78 complained of vestibular symptoms alone (39%), 31 combined vestibular and cochlear symptoms (15.5%) and 9 cochlear symptoms alone (4.5%). Likewise in Series II the symptoms were predominately vestibular, less frequently combined vestibular and cochlear, and rarely cochlear alone (*see* Table 4). The neuro-otological symptoms reported by the 35 tension headache patients were all vestibular with the exception of phonophobia which will be given separate consideration.

Severity of symptoms. Information about severity was obtained from all 118 migrainous patients of Series I. In 10, the vestibular symptoms were severe enough for the patient to seek medical help, compared with only one of the tension headache patients ($P < 0.05$).

Series II, as already stated, was wholly comprised of migrainous patients whose neuro-otological symptoms had at times been severe enough to warrant referral for neuro-otological examination.

Vestibular symptoms. Whether alone or accompanied by cochlear disturbances, vestibular symptoms were reported significantly more by the Series I migraine patients than by the tension headache group ($P < 0.001$) (Table 1).

The occurrence of *vertigo*, defined as an 'illusion of rotation of the environment or of the patient himself', was significantly higher in the Series I migraine patients than in the tension headache group ($P < 0.001$), whereas there was no significant difference in the occurrence of less well defined vestibular disturbances variously described as dizziness, giddiness, swimming sensation in the head, floating or sinking sensations or transitory feelings of being off balance, grouped for convenience as 'giddy sensations'. The occurrence of both types of vestibular symptoms in Series I migraine patients and tension headache patients are documented in Tables 1 and 2 and for Series II migraine patients in Table 4.

TABLE 1 VESTIBULAR SYMPTOMS IN PATIENTS WITH MIGRAINE AND TENSION HEADACHE

	Migraine $n = 200$	*Tension headache* $n = 116$
Vestibular symptoms (Total)	109 (54.5%)*	35 (30.2%)
Vertigo	53 (26.5%)*	9 (7.8%)
Giddy sensations	56 (28.0%)	26 (22.4%)

* $P < 0.001$.

TABLE 2. TEMPORAL RELATIONSHIP OF VESTIBULAR DISTURBANCES TO ATTACKS OF MIGRAINE AND TENSION HEADACHE

	Preceding		*During*		*Following*		*Headache-free period*	
Symptom	*Migraine*	*Tension headache*	*Migraine*	*Tension headache*	*Migraine*	*Tension headache*	*Migraine*	*Tension headache*
Vertigo	8 (4%)**	—	25 (12.5%)*	8 (6.9%)	1 (0.5%)	—	19 (9.5%)**	1 (0.86%)
Giddy sensations	17 (8.5%)	1 (0.86%)	30 (15%)	24 (20.7%)	3 (1.5%)	—	6 (3%)	1 (0.86%)
Total	25 (12.5%)***	1 (0.86%)	55 (27.5%)	32 (27.6%)	4 (2%)	—	25 (12.5%)***	2 (1.72%)

Migraine $n = 200$, tension headache $n = 116$ $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

None of the tension headache patients reported *cochlear symptoms* in the form of hearing loss, tinnitus or distortion of pitch, speech and sound localization. One or other of these symptoms or a combination of them were reported by a number of migrainous patients of Series I and II, either alone or combined with vestibular disturbances. The occurrence of cochlear disturbances in the Series I and II migraine patients is shown in Tables 3 and 4.

TABLE 3 TEMPORAL RELATIONSHIP OF DISTURBANCES OF HEARING TO ATTACKS OF MIGRAINE (OCCURRING IN 40 OF THE 200 PATIENTS OF SERIES I)

Cochlear symptom	*Total*	*Preceding*	*During*	*Following*	*Headache-free period*
Hearing loss	13	1	8	1	3
Tinnitus	29	3	15	—	11
Pitch distortion	8	1	6	—	1
Total	50*	5	29	1	15

Cochlear symptoms only: 9 patients; combined cochlear and vestibular symptoms: 31 patients;
* 10 patients had more than one cochlear symptom.

TABLE 4. NEURO-OTOLOGICAL SYMPTOMS OF SERIES II PATIENTS

		Group 1 Neuro-otological disturbances related to headache (44 patients)			*Group 2 Neuro-otological disturbances independent of headache (36 patients)*		
	Total	*Preceding (17)*	*During (25)*	*Following (2)*	*Unclassified (24)*	*Ménière's disease (6)*	*Positional vertigo/nystagmus (6)*
Vertigo							
Episodic	44	11	10	2	15	6	—
Postural or positional	14	—	3	—	5	—	6
Giddy sensations	21	7	10	—	4	—	—
Oscillopsia	1	—	1	—	—	—	—
Hearing loss							
Transitory	7	1	4	1	1	—	—
Persistent	6	—	—	—	2	4	—
Tinnitus							
Transitory	8	3	2	1	2	—	—
Persistent	7	—	—	—	2	5	—
Pitch distortion	3	—	2	—	1	—	—
Total	111*						
Disturbances of balance only			34			21	
Disturbances of hearing only			2			0	
Combined disturbances* of hearing and balance			8			15	
Total			44			36	

* 28 patients had more than one symptom

Phonophobia. Amongst the Series I patients, the most common symptom was phonophobia which nearly always accompanied the headache phase of the attacks and was experienced by 162 patients (81 %). Significantly it was reported by only 14 of the 116 (12.1 %) tension headache patients ($P < 0.001$). Some migrainous patients maintained that their hearing became more acute than normal during their headaches so that even the faintest noise or sound appeared to be louder and more disturbing. Paradoxically, 5 patients experienced phonophobia despite the fact that they admitted to some hearing loss during their attack of migraine.

Photophobia was described by 147 migrainous patients (73.5%) and was accompanied by phonophobia in all but 21.

History of motion sickness. A history of motion sickness was elicited from 77 of 152 Series I patients (50.7%) in contrast to 24 of the 116 tension headache group (20.1%) ($P < 0.001$).

Relationship of vestibulocochlear disturbances to time of attacks of headaches. In both Series I and II, vestibulocochlear disturbances occurred most commonly during the headache phase, less often preceding the headache as aura symptoms and/or during headache-free periods, and only rarely following the headache. In a few cases, however, some overlap occurred: thus 8 cases of Series I whose symptoms preceded the headache also experienced them at times independently of the headache. Vestibular symptoms in the patients with tension headache nearly always accompanied the headache. The relevant statistics are presented in Table 2 and reveal significant differences between tension headache and migraine. The relationship of cochlear disturbances to the time of attacks of migrainous headache of Series I patients is shown in Table 3.

A temporal relationship was established between symptoms and headache in 44 of the 80 patients of Series II. In the remaining 36 the symptoms occurred independently of the headache. These will be considered separately as groups 1 and 2, respectively. Group 1 can be divided into three subgroups (a) symptoms preceding headache—17 patients; (b) symptoms occurring during headache—25 patients; and (c) symptoms following headache—2 patients. Group 2 consists of three subgroups (a) unclassified vestibular and/or cochlear disturbances—24 patients; (b) patients with Ménière's disease—6 patients; and (c) patients with benign paroxysmal positional vertigo/nystagmus—6 patients.

The distribution of vestibulocochlear symptoms in groups 1 and 2 patients is presented in Table 4.

Migraine: Series I and II

The foregoing has identified significant differences between tension headache and migraine in several respects which mark them out as disparate populations. In the following, therefore, attention will be confined to the remaining findings of Series I and II.

Age of onset of vestibulocochlear symptoms and relationship to the onset of migraine. In Series I, the age of onset of the vestibular and/or cochlear symptoms was established in 99 patients. The distribution is given in fig. 1 which shows that there is a sharp peak in the third decade followed by a gentle fall in the fourth to seventh decades. Interestingly, males predominate in the second decade.

The evaluation of the interval between the onset of migraine and the onset of the neuro-otological disturbances revealed that the higher the age of onset of migraine, the shorter the interval between the two. In 24 patients the onset was simultaneous and before the age of adolescence in half of them. In four patients, episodic vertigo began first (in 2 before the age of 18 years) and migraine some years later.

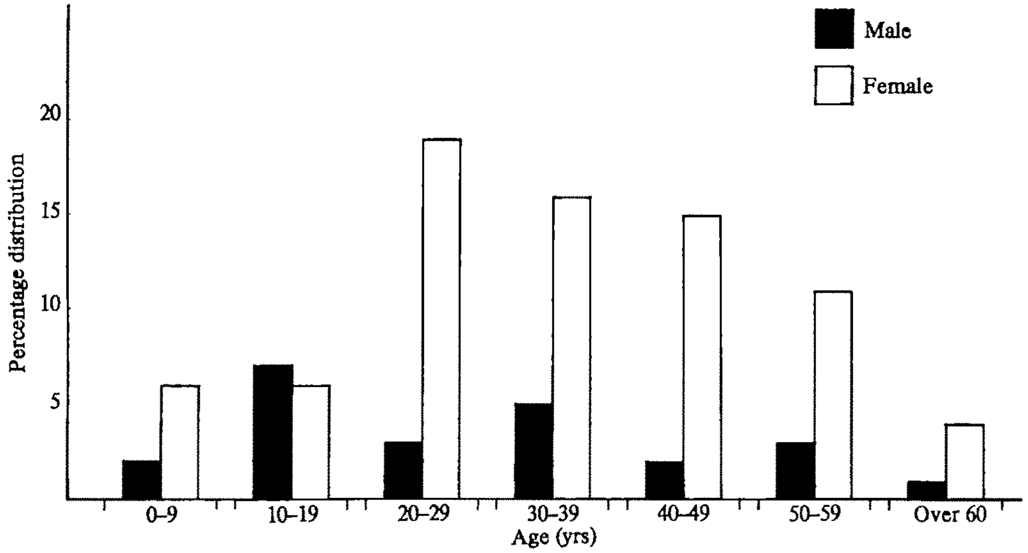

FIG. 1. Age at onset of neuro-otological symptoms in Series I.

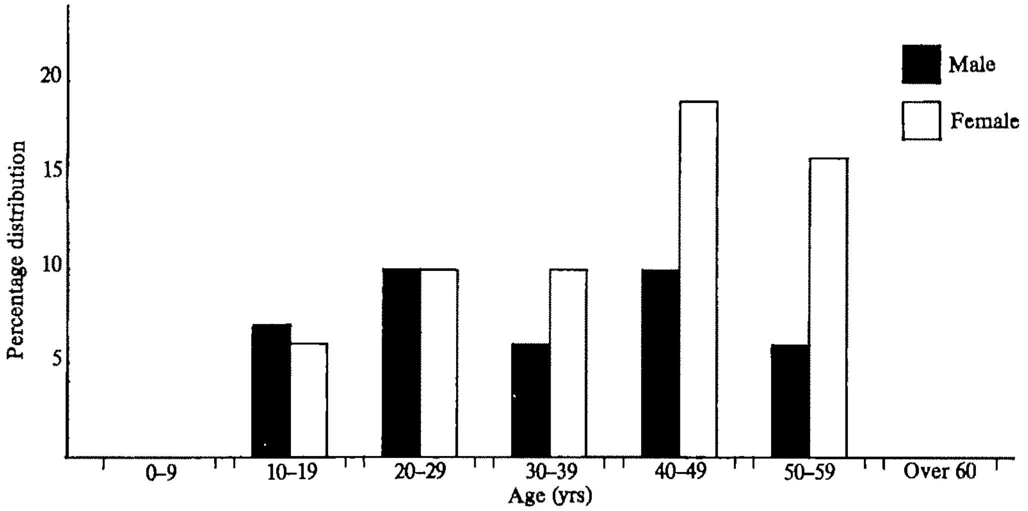

FIG. 2. Age at onset of neuro-otological symptoms in Series II.

In Series II, age of onset of the neuro-otological symptoms was established in 57 of the 80 patients. Fig. 2 shows that the overall incidence of males is higher than in a normal migrainous population, especially so in the younger age groups, while females predominate in the older age groups.

Commencement of vestibulocochlear disturbances was correlated with the time of onset of migraine in 5 of the group 1 patients and in 3 of the patients with unclassified vestibulocochlear disturbances of group 2. In the remaining patients their onset followed migraine at intervals from several months to years.

Duration of symptoms. The duration of the vestibulocochlear episodes varied from patient to patient and from attack to attack. Usually they were transitory, lasting seconds or minutes only, but they persisted for some hours in certain patients, and for a day or longer in a few. In all patients with Ménière's disease and benign paroxysmal positional vertigo/nystagmus the duration of vestibular and/or cochlear disturbances were in character with these disorders.

Frequency of the symptoms. In the majority of the patients of Series I and II the vestibulocochlear disturbances associated with the headache accompanied severe migrainous attacks. There were, however, an appreciable number of patients who experienced the symptoms with each or every other attack. In a few, the episode occurred only once. No particular periodicity pattern or time relationship was apparent in patients in either series in whom the vestibulocochlear symptoms occurred during the headache-free intervals.

Vestibular symptoms and their relation to head movement. Of the 109 patients of Series I with vestibular disturbances, in 50 these were brought on by positional changes of the head or adopting a certain posture. This was typically so in the patients with benign positional vertigo/nystagmus of Series II.

Initial clinical diagnosis. Of the 118 Series I patients with vestibulocochlear disturbances, 46 had classical migraine and 72 nonclassical. Of the remaining 82 without symptoms, 23 had classical and 59 nonclassical migraine. The incidence of classical migraine was higher by 11 per cent in the patients with symptoms than in those without.

It is of some interest that, in terms of the initial diagnosis, twice as many classical migraine sufferers experienced the disturbances preceding the headache as did the nonclassical.

In Series II, the types of migraine diagnosed clinically before referral for neuro-otological examination were: classical migraine, 41 patients; basilar artery migraine, 6 patients; ophthalmoplegic migraine, 2 patients; hemiplegic migraine, 1 patient; and nonclassical migraine, 30 patients. The occurrence of occipital pain or headache located elsewhere but affecting the occipital region was 32.5 per cent.

The distribution in groups 1 and 2 was as follows. In group I, of the 17 patients whose vestibulocochlear symptoms preceded the headache, 8 had classical, 3 basilar, 1 hemiplegic, 1 ophthalmoplegic and 4 nonclassical migraine. In patients with basilar, hemiplegic and ophthalmoplegic migraine, the possibility of a structural lesion had been excluded by neurological investigation including angiography. It is perhaps noteworthy that the patients with hemiplegic and ophthalmoplegic migraine experienced their symptoms only at the time of their migraine attacks when ophthalmoplegia or hemiplegia occurred. In patients with classical migraine the disturbances of hearing and/or balance occurred together with the visual or other focal neurological disturbances constituting the aura. In the 4 patients with nonclassical migraine, neuro-otological symptoms appeared shortly before the attacks of headaches as auras. Of the 25 patients in whom the symptoms accompanied the headache, 12 had classical, 1 ophthalmoplegic and 14 nonclassical migraine. The 2 patients in whom the disturbances followed the headache both had nonclassical migraine. For group II, 21 of the 36 patients had classical, 1 ophthalmoplegic and 14 nonclassical migraine.

TABLE 5 SUMMARY OF NEURO-OTOLOGICAL FINDINGS IN PATIENTS IN SERIES II

		Group 1 Neuro-otological disturbances related to headache (44 patients)			*Group 2 Neuro-otological disturbances independent of headache (36 patients)*		
	Total	*Preceding (17)*	*During (25)*	*Following (2)*	*Unclassified (24)*	*Ménière's disease (6)*	*Benign positional vertigo/nystagmus (6)*
Neuro-otological signs							
Positive Romberg	7	4	1	—	2	—	—
Impaired gait (eyes closed)	18	10	6	—	2	—	—
Spontaneous nystagmus	4	1	—	—	3	—	—
Unsteadiness of lateral gaze	2	1	1	—	—	—	—
Positional nystagmus							
Peripheral	4	—	—	—	—	—	4
Central	1	—	—	—	1	—	—
Abnormal optokinetic nystagmus (directional preponderance)	11	3	5	—	3	—	—
Caloric test abnormalities	51	13	12	1	15	6	4
Sensorineural hearing loss	22	5	3	—	6	6	2
Total	120*						
Patients with no neuro-otological signs		1	11	1	5	—	—
Patients with neuro-otological signs		16	14	1	19	6	6
Impaired vestibular function only			24			19	
Impaired cochlear function only			0			1	
Combined impairment of cochlear and vestibular function			7			11	
		Total	31			31	

* 58 patients had more than one sign

Neuro-otological signs (*Series II*). Neuro-otological abnormalities were identified in 62 of the 80 patients in groups 1 and 2 and are summarized in Table 5. Impairment of gait was defined as an obvious deviation to right or left on walking with eyes closed, while a positive Romberg's test in this context implies a pronounced bodysway to one or other side on standing with feet together and eyes closed. The caloric abnormalities took the form of either canal paresis or directional preponderance or a combination of both. General reduction of the responses was found in a few patients and an enhancement of the responses in 2. The latter cannot be taken to be a manifestation of cerebellar involvement since it was accompanied by nausea and vomiting. Details of caloric test findings are shown in Table 6.

Neuro-otological signs in group 1 patients. Sensorineural deafness was found in 8 patients; of these 1 had complete and 1 partial loudness recruitment, suggesting pathology affecting the cochlear endorgan. In the remainder in whom the loudness

TABLE 6 SUMMARY OF CALORIC RESPONSES IN PATIENTS IN SERIES II

		Group 1 Neuro-otological disturbances related to headache (44 patients)			*Group 2 Neuro-otological disturbances independent of headache (36 patients)*		
No of patients	*Total (80)*	*Preceding (17)*	*During (25)*	*Following (2)*	*Unclassified (24)*	*Ménière's disease (6)*	*Positional vertigo/nystagmus (6)*
Unilateral canal paresis (CP)	19	1	5	—	10	3	—
Bilateral canal paresis	9	3	2	—	2	1	1
Directional preponderance (DP)	14	7	4	—	1	1	1
Combined CP and DP	6	—	—	1	2	1	2
Enhancement of responses	2	2	—	—	—	—	—
Perverted caloric nystagmus	1	—	1	—	—	—	—
Normal	29	4	13	1	9	—	2
Total abnormalities	51	13	12	1	15	6	4

recruitment tests could not be performed, the deafness was chiefly for high tones, either unilateral or bilaterally symmetrical.

Of the 31 patients with positive neuro-otological signs, the evidence pointed to a central lesion in 11, a peripheral lesion in 6 and was indeterminate in 14.

Neuro-otological signs in group 2 patients. There was clinical evidence of neuro-otological abnormality in 19 of the 24 patients with unclassified vestibulocochlear disturbance. The neuro-otological signs, taken together with the symptoms, suggested peripheral pathology in 5 and central pathology in 4, the remaining 10 being difficult to specify. In all the patients with Ménière's disease and positional vertigo/nystagmus of benign paroxysmal type, the signs and symptoms were characteristic of the respective disorders according to accepted criteria (Dix and Hallpike, 1952). Localization based upon neuro-otological findings in group 1 and 2 patients is shown in Table 7.

TABLE 7 NEURO-OTOLOGICAL LOCALIZATION OF LESION IN PATIENTS IN SERIES II

		Group 1 Neuro-otological disturbances related to headache (44 patients)			*Group 2 Neuro-otological disturbances independent of headache (36 patients)*		
No of patients	*Total (80)*	*Preceding (17)*	*During (25)*	*Following (2)*	*Unclassified (24)*	*Ménière's disease (6)*	*Positional vertigo/nystagmus (6)*
Central	15	4	7	—	4	—	—
Peripheral	23	4	1	1	5	6	6
Inconclusive	24	8	6	—	10	—	—
Total abnormalities	62	16	14	1	19	6	6

Laterality of vestibulocochlear derangements and headache. Of 18 patients of group 1 with unilateral derangements, the headache was ipsilateral in 4, contralateral in 4 and either bilateral or alternating in the remainder. This same lack of correlation was also apparent in patients of group 2. Thus of 10 of the 24 patients with unclassified unilateral pathology, the headache was ipsilateral in 1, contralateral in another and either alternating or bilateral in the remainder.

DISCUSSION

Vestibular and/or cochlear symptoms were described by 59 per cent of the 200 unselected migraine sufferers interviewed; in 39 per cent these symptoms were mild, moderate in 14.5 per cent and severe in 5 per cent. Other authors have reported an incidence varying between 5 to 78 per cent (Selby and Lance, 1960; Lance and Anthony, 1966; Barolin, 1969; Fedorova, 1970; Kuritzky *et al.*, 1981*b*). None, however, have commented upon the severity of symptoms. In 5 per cent of the cases in the present study the disturbances were severe enough for the patient to seek medical advice and were frequently more disabling than the headache. The presumption is that they comprise the migrainous population represented by the patients in Series II.

Comparison with patients with tension headache has shown that there are important differences in the two groups in terms of the incidence and severity of vestibular disturbances and their time of onset in relation to the headache. Indeed, the findings in respect of tension headache are not dissimilar to those reported by Hinchcliffe (1961) in a normal rural population of 800.

Disturbances of balance and/or hearing associated with attacks of migraine occurred most commonly during the headache, less commonly preceding the headache, and rarely following the headache. In addition a proportion of patients experienced attacks of vertigo during headache-free periods.

Symptoms Preceding Headache

A total of 12.5 per cent of patients in Series I and 21.25 per cent of Series II experienced their symptoms as auras preceding the headache. Since the labyrinths, the eighth nerve trunk, its nuclei and their connections in the CNS (with the exception of the cortical areas) are all supplied by the branches of the vertebral and basilar arteries, an initial vasoconstriction in these territories, together with consequent ischaemia of the relevant regions would, on the available evidence (Skinhøj, 1973), appear to be the most likely explanation for the preheadache vestibulocochlear disturbances of either peripheral or central origin. In a number of patients in both series these disturbances were accompanied by visual or other types of migrainous aura as reported by Watson and Steele (1974) in children, thus incriminating more than one intracranial arterial territory. These, according to the definition of the Ad Hoc Committee on Classification of Headache (1962), would be diagnosed as 'classical migraine'. Attacks preceded only by vestibular and/or cochlear disturbances customarily have been included in the category of 'non-classical' or 'common' migraine. Since, however, these imply focal nervous dysfunction it would seem more logical to regard them as 'classical' migraine or, more specifically, as a partial form of 'basilar artery migraine'.

Symptoms During Headache Phase

Of all the patients with neuro-otological disturbances, 27.5 per cent in Series I and 31 per cent in Series II experienced them during the headache phase.

The most persuasive explanation for the focal neurological disturbances, including vertiginous episodes, occurring during the headache phase has been given by Kuritzky *et al.* (1981*a*, *b*) who maintained 'that prolonged vaso-constriction and opening of arterio-venous shuntings may decrease the blood supply to the labyrinths, cause ischaemia and affect the secretion or absorption of the endolymph and perilymph'. Skinhøj (1973) has demonstrated a considerable reduction of cerebral blood flow during the headache phase, probably of sufficient degree to cause ischaemia and lactate acidosis while Jensen *et al.* (1981) found angiographic evidence of marked and prolonged vasospasm of the basilar artery together with vertebrobasilar dysfunction and brainstem involvement in a case of hemiplegic migraine.

The prolonged vasoconstriction of vertebral and basilar arteries could readily account for the vestibular disturbances of both peripheral and central origin occurring during the headache phase. Alternative mechanisms giving rise to brainstem and cranial nerve disturbances (Wolff, 1963) that have been suggested include direct mechanical pressure by dilated oedematous arteries upon cranial nerves and a transudation of oedematous fluid within the nervous system causing not only mechanical interference but also affecting the functional capacity of neurons. In addition, the respective roles of vasoactive transmitters in 'spreading oligaemia' (Olesen *et al.*, 1981) and disturbed serotonin levels on synaptic function (Kuritzky *et al.*, 1981*a*) deserve further study.

Symptoms in Headache-free Periods

A total of 12.5 per cent of patients in Series I and 45 per cent of Series II experienced disturbances independent of the headache. Moreover, in 8 of the former and 3 of the latter, they were accompanied by the patient's usual migrainous visual or other aura but without ensuing headache. These patients represent a typical form of 'migraine without headache' (Whitty, 1967), a term to be preferred to 'migraine equivalent' which includes migraine precursors such as 'bilious attacks'. The patients with unclassified disturbances represent a special group which will be considered later.

Interval between Onset of Migraine and Onset of Neuro-otological Manifestations

In the majority of patients of Series I, headaches predated the disturbances by 1 to 54 years, and in consequence a connection with migraine cannot be inferred with any certainty. In 24, however, the onset was simultaneous and it is noteworthy that in more than half, it occurred before adolescence, strongly suggesting a close relationship between the two. In 4 patients episodic vertigo commenced first (before the age of 18 years in 2) and migrainous attacks some years later; in these the possibility of the vertigo being a migraine precursor or 'equivalent' has to be considered. Fenichel (1967) reported 2 siblings with benign paroxysmal vertigo in childhood which gradually developed into migrainous headaches, and Watson and Steele's (1974) 9 children with paroxysmal dysequilibrium later developed classical migraine.

The syndrome 'benign paroxysmal vertigo of childhood' described by Basser (1964) is regarded as a migraine equivalent by some authors (Koenigsberger *et al.*, 1970; Koehler, 1980), but this requires further support by long-term follow-up studies.

Persisting Vestibulocochlear Dysfunction

Few reports have appeared in the literature of the results of systematic neuro-otological investigations carried out upon patients with migraine.

In Series II, findings indicative of definite dysfunction of the vestibular and/or cochlear systems were present in 62 of 80 patients (77.5%), half with central and half with peripheral pathology. This high incidence can be attributed to the fact that the patients were referred on account of their symptoms for neuro-otological examination which was likely to be more searching than a routine neurological examination.

Since Féré's time (1881, 1883; cited in Sachs, 1970), it has been recognized that migrainous attacks can give rise to permanent damage to the nervous system and reports have appeared of persisting visual defects, damage to the brainstem and other neurological deficits involving certain cranial nerves (Connor, 1962; Pearce, 1968). More recently Dürsteler (1975), Kuritzky *et al.* (1981*a*), Toglia *et al.* (1981) and Eviatar (1981) have commented upon a high incidence of electronystagmographic abnormalities. In the light of this and other evidence (Hungerford *et al.*, 1976; Solomon and Spaccavento, 1982; Hauge, 1954; Skinhøj, 1973), the consensus of opinion is that most migrainous complications are caused by ischaemia of sufficient severity to produce infarction of nervous tissue occurring during the vasoconstrictive phase of the attack. This is further supported by our finding that 16 of the 17 patients whose disturbances occurred during the preheadache phase of migraine showed evidence of persisting dysfunction of the vestibulocochlear system in contrast to only 14 of 25 patients who experienced symptoms during the headache phase.

Migraine and Phonophobia

One of the most striking findings in the Series I patients is that 81 per cent reported phonophobia as an accompaniment of the headache. Suggestions that this phenomenon is due to increased excitability (Sachs, 1970) or hyperactivity of the special senses (Lance, 1969) are difficult to relate to the fact that the limit of normal cochlear sensitivity is constrained by physical factors involving Brownian motion, and although no threshold audiometric studies have been performed, it seems unlikely that hearing acuity can be enhanced. By contrast, it is well known that a constant accompaniment of cochlear pathology apart from hearing loss is the presence of 'loudness recruitment'; indeed there is some evidence that it precedes the hearing loss (Hallpike and Hood, 1959). The essence of this phenomenon is an abnormally rapid increase in loudness with increase in intensity of sound. As a result, despite the deafness, more intense sounds may be heard with normal or above normal loudness and a feature of this condition is intolerance of loud noise. This would seem to be closely akin to phonophobia and raises the question as to whether or not it has the same underlying pathology. It is of particular note in this respect that hearing loss was present in 5 patients with phonophobia. In addition, the incidence of phonophobia in patients with neuro-otological disturbances (86%) was higher than in those without (74%). Present evidence, therefore, strongly suggests that phonophobia may be a manifestation of loudness recruitment and accordingly results from a transient disturbance of function of the cochlear receptors occurring nearly always during the headache phase of the attack. This raises the interesting concept that migraine with phonophobia might be considered to fall within the classification of classical migraine (Ad Hoc Committee for the Classification of Headache, 1962).

Migraine and Motion Sickness

As many as 50.7 per cent of the Series I patients with migraine were subject to motion sickness in contrast to 20.1 per cent of the patients with tension headache. Symonds (1926) was the first to draw attention to the relationship between migraine and motion sickness; he thought that this was due to a failure of the co-ordinating centres to compensate for labyrinthine overstimulation. Although this notion prevailed for many years, recent consensus of opinion inclines to the view that it results from a 'mismatch' between vestibular, visual and proprioceptive input (Money, 1970; Brandt *et al.*, 1973; Reason, 1978; Jay and Jay, 1981). Estimates of the incidence of motion sickness in migraine sufferers vary between 26 (Childs and Sweetnam, 1961) and 60 per cent (Pearce, 1971), in contrast to 7.8 (Childs and Sweetnam, 1961) and 24 per cent (Kuritzky *et al.*, 1981*b*) in normal control groups. There can be no question on the basis of our own findings and those of others that the incidence of motion sickness is unusually high in migraine sufferers. Although account has to be taken of the suggestion that both have certain common features in respect of their personality profiles, a more direct link seems inescapable.

Relation to Postural or Positional Changes

In nearly half of the patients vestibular symptoms were brought on by or made worse by positional changes of the head or by postural changes and the majority maintained that this occurred during their headaches.

Although gross vestibular signs are rare, electronystagmographic evidence of vestibular dysfunction is fairly common; reported abnormalities varying from 57 to 80 per cent (Dürsteler, 1975; Raffaelli and Menon, 1975; Kuritzky *et al.*, 1981*a*; Toglia *et al.*, 1981). In the presence of asymptomatic vestibular pathology, vascular changes occurring during the headache phase might well provoke instability exacerbated by postural and head position changes.

Migraine and Ménière's Disease

Six patients developed Ménière's disease at varying intervals of years after the onset of migraine. A link between migraine and Ménière's disease has been postulated by many authors who have drawn attention to the high incidence of personal and family histories of migraine in cases of this disease (Symonds, 1926; Atkinson, 1943, 1944; Hinchcliffe, 1967*a*, *b*). According to C. P. Symonds (1972, personal communication) and Atkinson (1943, 1944) there is a correspondence not only in the laterality of the deafness and the migrainous headache, but also in the occurrence of headache and attacks of Ménière's disease. Furthermore, Atkinson reported that the treatment for Ménière's attacks also relieved migraine headaches (Atkinson, 1943, 1944).

Although its true incidence in the UK is not known, it is now generally agreed that Ménière's disease as diagnosed according to modern criteria is a rare condition. Of the 500 case records of patients with multiple sclerosis investigated neuro-otologically, representing all age groups, and predominantly with complaints of vertigo, no single case was found. In addition, we have, by way of comparison, reviewed the last 100 patients seen in the Neuro-Otology clinic whose only presenting complaint was vertigo with or without hearing loss. Among the more common diagnoses were vertebrobasilar insufficiency, benign positional or paroxysmal vertigo, vestibular neuronitis, and head injury. Ménière's disease, however, was thought to be the definite diagnosis in only 1 patient and suspected in another. By contrast, an association with migraine was suspected in 4 patients and clearly established in 3. This is fairly persuasive evidence and suggests that a connection between Ménière's disease and migraine in the present series is more than coincidence.

The pathology of Ménière's disease has been clearly described as paroxysmal endolymphatic hydrops associated with organic derangement of the end organs (Hallpike and Cairns, 1938). Its aetiology is less clear although as with migraine, a paroxysmal vasomotor disorder is thought to be responsible (Seymour, 1960). Fowler and Zeckel (1952) demonstrated narrowing of blood vessels and blood sludging during the vertiginous attacks of Ménière's disease. There is evidence that psychological factors are involved in Ménière's disease and migraine, with both conditions manifesting an abnormal vasomotor response to stress situations. Both migraine and Ménière's disease sufferers have certain common features in respect of their personality profiles (Hinchcliffe, 1967*b*). The selection of a population of migraine sufferers will therefore inevitably be more heavily weighted to the inclusion of patients with Ménière's disease than would a normal population and this is certainly a factor that needs to be taken into account.

Migraine and Benign Paroxysmal Positional Vertigo/Nystagmus

Six cases of benign paroxysmal positional vertigo were found among the 80 migraine sufferers and significantly 3 experienced some of their attacks in association with the migrainous headache. Similar findings have been reported by Schiller and Hedberg (1960) and Slater (1979). One of the causes of benign paroxysmal positional vertigo/nystagmus is held to be vascular occlusion involving the otolith apparatus (Dix and Hallpike, 1952) and it seems possible that this could be brought about as a result of, or in association with, attacks of migraine.

Unclassified Disturbances Occurring Independently of the Headache

This group of patients (numbering 24 in our series) and characterized by recurrent attacks of vertigo, usually without cochlear involvement, and occurring independently of the headache, deserves special consideration because it is one that has attracted particular comment in recent years. Slater (1979) was the first to draw attention to an association of a condition that he labelled 'benign recurrent vertigo' with migraine which led him to postulate that it was a form of migraine. Similar case histories and conclusions have subsequently been reported by Moretti *et al.* (1980) and Behan and Carlin (1982). Interestingly, the latter additionally reported that the patients in their series responded well to the administration of pizotifen, a preparation used in the prophylactic treatment of migraine.

A distinguishing feature of all patients reported (9 males and 35 females) from those in our series was that in the majority the diagnosis of migraine was inferred from a family history or headache associated with the attacks of vertigo. In Behan and Carlin's series, for example, only 30 per cent of 32 patients actually complained of headache while 19 patients had a family history of migraine. Of special note was their finding that half of the patients complained of visual disturbances of one kind or another, although their association with the vertigo is not specified. One surprising feature is that all authors agree that despite the fact that spontaneous or positional nystagmus are consistently revealed on electronystagmographic examination, caloric abnormalities are conspicuous by their absence; indeed this would seem to be a determining factor in the differential diagnosis of the condition.

Since the patients in our series differ in certain important respects, it is perhaps worth considering them in more detail. In the first place there was no predominance of females, there being 13 males and 11 females with ages ranging from 22 to 53 years (average age 41.8 years). Ten patients had a family history of migraine in parents or siblings; 15 patients had classical, 8 nonclassical and 1 ophthalmoplegic migraine. Only 1 patient experienced visual symptoms at the time of the vertiginous attack. The duration of the vestibular disturbances varied between 1 to 3 min and 3 days with a frequency ranging from several times a week to four times in three years. In the majority, the attacks had persisted over very many years with an average of ten years. Nineteen patients had clear neuro-otological signs (*see* Table 5), there being definite caloric abnormalities in no fewer than 15. The pathology was thought to be central in 4, peripheral in 5, and inconclusive in the remainder. As to differential diagnosis, as usual this is a matter of some speculation, but four broad categories can be identified. (1) Eight patients with normal caloric responses and unimpaired cochlear function would seem, on the available evidence, to conform to Slater's (1979) definition of benign recurrent vertigo. (2) Vestibular neuronitis was originally suspected in 8 patients with definite caloric abnormalities and no cochlear symptoms. In one of these the vertiginous attack immediately followed the migrainous attack. However, the time course of the disease and the absence of any evidence of focal infection are at odds with the description, originally given by Dix and Hallpike (1952). Instead they are more in accord with a condition symptomatically similar to vestibular neuronitis but considered by Millikan *et al.* (1959) to result from occlusion of the labyrinthine division of the internal auditory artery affecting the vestibular receptors in the labyrinth. (3) Four patients presented with both cochlear and vestibular signs and symptoms, 2 with tinnitus and 2 with hearing loss. In some of these at least, the diagnosis of early Ménière's disease is a possibility. (4) In 4 patients there was clear neuro-otological evidence of central pathology.

Although the association of migraine with the occurrence of vestibulocochlear disorders is self-evident in the patients in group 1, it is less obvious in this unclassified group. A feature common to both, however, as will be seen from Tables 5 and 6, is the similar distribution in nearly three-quarters of each of positive neuro-otological findings indicative of underlying pathology. It is probable that vasoconstriction in the vertebrobasilar territory, together with subsequent ischaemia of the relevant regions, is the causative factor responsible for both central and peripheral damage in respect of the patients in group 1 and hence, by analogy, with the patients in the unclassified group. Beyond this little more can be said at the moment. What is now needed is information relating the prevalence of migraine in an appropriately categorized vertiginous population attending a neuro-otology clinic and motivated by these findings we now propose to undertake a prospective study of this kind.

ACKNOWLEDGEMENTS

Acknowledgements are made to the Migraine Trust and the Wellcome Foundation for financial support. We thank Drs Marcia I. P. Wilkinson, K. J. Zilkha, J. N. Blau and M. R. Dix for allowing us to see their patients and for their helpful guidance during the course of the investigations.

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(*Received April 21, 1983. Revised May 17, 1984*)

Brain (1984), **107**, 1143-1163

VISUAL STABILIZATION OF POSTURE

PHYSIOLOGICAL STIMULUS CHARACTERISTICS AND CLINICAL ASPECTS

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SUMMARY

Visual stabilization of posture is critically dependent on stimulus characteristics as well as on the performance of the visual system. The purpose of the present investigation was to obtain quantitative data in man by means of posturography of fore-aft and lateral body sway in relation to different visual stimulus characteristics.

Visual acuity, when decreased logarithmically, causes a linearly increasing postural instability, twice as prominent for fore-aft than for lateral sway. Any measurable visual contribution for fore-aft sway ceases with an acuity lower than 0.03 and for lateral sway with an acuity lower than 0.01.

The central area of the visual field as compared with the peripheral retina dominates postural control. The foveal region exhibits a powerful contribution, in particular for lateral sway.

A partial but significant visual stabilization is preserved with a visual input rate between 1 to 4 Hz flicker frequency. As soon as continuous motion perception becomes involved with frequencies higher than 4 Hz, visual stabilization gradually improves with a saturation at frequencies higher than 16 Hz.

Lateral body sway activity and eye-object distance are linearly related: body sway decreases with increasing distance corresponding to the linear decrease of net retinal displacement with increasing eye-object distance.

Aspects of 'afferent' and 'efferent' visual motion perception, which involve fore-aft and lateral body sway differently, are evaluated. The clinical relevance is demonstrated in patients with oculomotor disturbances. The results are discussed with respect to the variety of related clinical disorders, which involve reduction in visual acuity, field defects, accommodation disturbances and ocular oscillations.

INTRODUCTION

Vision plays a major role in the multisensory process of postural stabilization. Physiologically it attenuates self-generated body sway by 50 per cent (Travis, 1945; Edwards, 1946) and clinically its effect on postural stability accounts for the significance of the Romberg test (Romberg, 1846) in patients suffering from either proprioceptive sensory dysfunction or cerebellar ataxia.

Optimal balance requires the continuous monitoring of the reafferent sensory consequences of body sway. The functional ranges of the main individual sensory systems—vestibular, somatosensory, visual—overlap, which enables them to compensate partially for mutual deficiencies. Postural imbalance induced either by sensory dysfunction or by inadequate stimulation arises from an intersensory mismatch, with information from one system at variance with the others. The intensity of postural imbalance is a function of the magnitude of the mismatch and is further increased if appropriate afferent information is eliminated such as on eye closure with an acute unilateral labyrinthine lesion (Brandt and Daroff, 1980). Nashner *et al.* (1982) assumed a dominant hierarchical influence of the vestibular system, this serving as a fixed orientation reference while vision, in normal subjects, subserves fine tuning of posture on the basis of the vestibular reference value within this multiloop control.

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Unlike vestibular stimuli, which invariably lead to the sensation of body motion (and therefore require a postural reaction in order to maintain balance), visual stimuli provide for two perceptual interpretations: either self-motion or object-motion. The decisive visual signal that starts active postural correction of body tilt may be dependent either upon relative image shift on the retina of the stationary visual surroundings or on 'efferent motion perception' when fixating stationary targets.

For a given head displacement, however, relative visual cues to enable adequate perception of this movement may be different in quality depending on the structure and illumination conditions of the visible surroundings as well as on the characteristics of the optical and the visual system.

Two phenomena may serve to illustrate the differential effects of visual conditions. (1) Angular displacement (α) on the retina is smaller, the greater the distance from the faced objects. Simple geometrical analysis indicates that in order to be detected visually, body sway must increase with increasing distance between the eyes and the nearest stationary visual contrasts, a mechanism which accounts for the occurrence of physiological postural imbalance under conditions that induce height vertigo (Bles *et al.*, 1980; Brandt *et al.*, 1980). (2) That it is possible to balance and to walk while reading demonstrates that focal and ambient visual functions can be dissociated. Even though pattern recognition and attention are dominated by the reading material, orientation in space and postural control are carried out sufficiently on the basis of peripheral visual stimuli at a subconscious level (Leibowitz *et al.*, 1982).

Although it is possible to maintain upright posture with closed eyes under ordinary conditions, vision plays its dominant role in patients with defects of the vestibular or somatosensory systems, as well as in normal subjects when performing more demanding balancing tasks such as sports or riding a bicycle.

During locomotion, evasion of obstacles and gross spatial orientation can be adequately performed even with a low visual acuity of 0.01 and with central and peripheral visual field defects. However, visual acuity as well as the area and location of the visual field play a significant role at least in fine tuning of posture, as will be demonstrated here.

While the amplitude, duration and direction of body acceleration clearly define a vestibular stimulus, the variability of visual motion stimuli gives rise to greater complexity. Visual perception of relative motion due to head sway is determined by the three-dimensional structure of the environment, as well as by the viewing conditions such as illumination or accommodation. Additional factors such as visual acuity, the location and size of the stimulus within the visual field, changing eye-target distances and therefore different retinal velocities, can all be involved in varying combinations.

The purpose of this investigation was to obtain quantitative data of fore-aft and lateral body sway in man in relation to critical visual stimulus characteristics such as visual acuity, accommodation, eye-object distance, area and retinal location of the visual scene, number and location of single stationary contrasts within the visual field and finally, the effect of stroboscopic surround illumination with impaired motion perception. It will be demonstrated how differential characteristics of the visual stimuli affect postural balance. The physiological data will also be used to advance an explanation for the pathogenesis of visual ataxia in patients with refractive errors or acquired ocular motor disorders.

METHODS

Apparatus and Data Analysis

The fore-aft and lateral body sway with free stance was measured simultaneously by the use of a stabilometer platform which transduces force changes exerted on the foot support (torque about the ankles and reaction forces at the feet). This procedure therefore does not measure simply the 'static' net displacement of the centre of gravity of the body but also dynamic components due to body inertia. The latter apparently enhance sway amplitudes predominantly at higher frequencies: the dynamic component accounts for less than 10 per cent of the force obtained at 0.2 Hz but 50 per cent at 0.5 Hz (Gurfinkel, 1973).

Subjects were placed on the force-measuring platform and were tested for body sway with free stance under different conditions with the eyes either open or closed. They were instructed to maintain optimal balance with a fixed preset foot position. A slab of foam rubber (height 10 cm, specific weight 40 g/cm^3) was placed on top of the stabilometer platform and covered by a second rigid foot support. This was to reduce the somatosensory contribution (ankle joint receptors) to postural control and therefore to enhance (disproportionately) the sensorial weighting of the vestibular and visual system, which were to be investigated.

A digital computer (Intertechnique IN 110) was used for analysis of 60 s segments of sway measurements (high pass filter 0.09 Hz, 60 dB/decade; sample interval 50 ms; upper frequency cut off 40 Hz, 60 dB/decade).

The root mean square values ($y_i = (n^{-1} \sum_{i=1}^{n} x_i^2)^{\frac{1}{2}}$) were selected as criteria for evaluation of postural stability. Although Fourier analysis is now very common, it requires periodicity of the stabilogram, which is unlikely to be achieved during a 1 min registration period. Without periodicity this method is difficult to interpret because it may introduce frequency components not present in the original recording. The root mean square (RMS) represents a suitable measure for average body sway over a certain period and allows an easy comparison to be made between the effects of different experimental conditions (Bles *et al.*, 1980).

Visual Stimulation

The normal 'eyes open' condition in front of a flat-structured screen at a distance of 100 cm to the eyes served as a standard measure with the individual RMS values of body sway set as 100 per cent. The screen was covered randomly with different coloured dots of different size (0.05 to 1 cm in diameter). With this arrangement linear horizontal or vertical structures were avoided. The normal room illumination provided a luminance level of about 40 cd/m^2. The particular viewing conditions for the different experiments are described within each experimental section.

RESULTS

Visual Acuity (*Experiment 1*)

A normal or sufficient visual acuity (VA) is a necessary prerequisite for common high frequency visual performances such as pattern recognition and reading. Despite the practical relevance of visual acuity for high frequency visual function (e.g., even minor deficits in VA due to errors of refraction are commonly corrected), its possible consequences for dynamic spatial orientation, perception of self-motion and particularly for postural control should not be neglected.

Method. The purpose of the first experiment was to assess the relationship between reduction in visual acuity and postural balance. Visual acuity was systematically diminished in controlled steps by semitransparent plastic foils, normally used for penalization of one eye in children with squint amblyopia. The foils were attached close to both eyes of each subject to obtain a generalized whole-field reduction in visual acuity without restriction of the visual field, giving acuities of 0.6, 0.3, 0.1, 0.03 and 0.01. Their different effects on posture were compared with the two extreme conditions of reference *eyes open, visual acuity 1.0* and *eyes closed*, respectively.

Visual acuity of 1 is defined by detectability of a gap of 1 min of arc in a Landolt C ring, which at a distance of 6 m corresponds to a gap of 1.75 mm. With an acuity of 0.1 this gap can be detected at 60 cm, and with an acuity of 0.01 at 6 cm. The diameter of the smallest cones in the human fovea is 0.5 min of arc, corresponding to 2.0–2.5 μm (1 min of arc = 4.85 μm in the human retina (Pirenne, 1967)).

Twelve healthy subjects (mean age 22.4 ± 4.5 years) were investigated; 5 of them usually wore glasses for correction of myopia. All measurements were obtained with glasses in these 5 subjects; one assessment without glasses was added.

Results. Fig. 1 shows the results for this experimental protocol. Decreasing visual acuity causes a gradual increasing postural instability of about 40 to 60 per cent with visual acuities of 0.1 and 0.03, respectively. The decrease in balance is significant at a confidence level of 99 per cent for all acuity steps tested, but quantitatively moderate with slight reductions in visual acuities to 0.6 and 0.3. The considerable instability with VA = 0.01 for eyes closed and for eyes open indicates in each case that a whole-field reduction of visual acuity below 0.01 for lateral, and below 0.03 for fore-aft body sway, eliminates the visual contribution to postural reactions during free stance in man.

The accentuated decrease in postural capability with lower visual acuities may be expressed in terms of a logarithmic equation for lateral (Eq. 1a) and fore-aft (Eq. 1b) body sway (correlation coefficient 0.98), derived from the data of fig. 1.

$$Y_l = 97.3 - 26.8 * \ln(X) \qquad (1a)$$

$$Y_{fa} = 85.2 - 49.1 * \ln(X) \qquad (1b)$$

Y represents percentage body sway relative to the standard situation (100 per cent) with a visual acuity of 1.0, and X represents visual acuity. Increase in fore-aft sway with decreasing visual acuity is almost twice as steep. This indicates higher visual requirements for optimal balance as compared with lateral sway, even with respect to the physiologically greater fore-aft sway amplitudes.

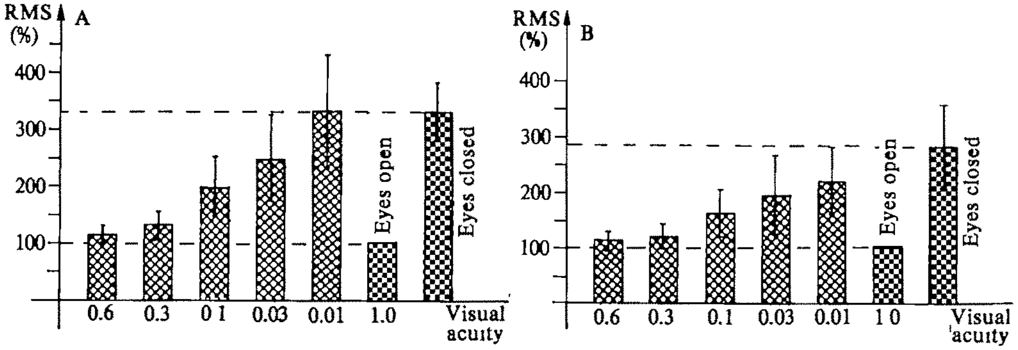

FIG. 1 Influence of visual acuity on lateral and fore-aft postural sway produced by occlusion of both eyes with plastic foils, giving visual acuities of 0.6, 0.3, 0.1, 0.03 and 0.01. The figure encompasses fore-aft (A) as well as lateral (B) body sway. Visual acuity, when decreased logarithmically, causes a linearly increasing postural instability. With visual acuities lower than 0.01 for lateral and 0.03 for fore-aft sway, visual stabilization ceases so that body sway is indistinguishable from the 'eyes-closed' situation.

In the experimental condition with visual acuity diminished by 99 per cent, visual orientation in space was not as severely affected during walking as might be inferred from the postural data. The subjects felt unstable during locomotion but usually were able properly to avoid major obstacles in the environment.

Comment and clinical relevance. Many patients with decreased visual acuity complain about postural instability, particularly at the beginning of sudden events. Stepwise changes of VA occur in patients with refractive errors who alternately use spectacles or not. Significant instability was found with spectacles off in 5 myopic subjects (degree of myopia in 4 subjects −3 to −5 dioptres (dpt), in 1 subject −11 dpt) within the group of the 12 normal subjects involved in Experiment 1, although subjectively they usually were unaware of the affect on balance skill. The normal ratio between RMS values with eyes open as compared to eyes closed of about 3.5 to 1 (fig. 1) shrank to a mean value of about 2.8 to 1.

Patients with aphakia from cataract surgery without refractive correction were demonstrated to have no measurable visual stabilization of postural sway as compared with upright stance with eyes closed (Brandt *et al.*, 1982). 'Defocus' primarily causes a reduction in VA with a consequent increase in postural sway. A semilogarithmic function characterizes the relationship between visual acuity and defocusing in dioptres (Laurance, 1926, cited by Westheimer, 1981). 'Defocus' of 1 dpt reduces VA from 100 per cent to 30 per cent, 'defocus' of 2 dpt to 15 per cent. According to this relationship VA in uncorrected aphakic patients is less than 0.01 and consequently their inability for fine visual tuning of posture is consistent with our results as indicated by Eq. (1).

Problems of stabilization may also arise in patients with anisometropia, when the retinal image size differs more than 5 per cent, and in patients with unilateral aphakia, who appear to be able to take advantage of the good retinal image in the corrected aphakic eye whilst suppressing the image of the phakic eye (Obstfeld, 1978). Spectacles cause a magnification of 15 to 25 per cent, and the different sized retinal images of both eyes will cause an insurmountable perception problem for single binocular vision (Obstfeld, 1978). Since the aphakic eye is unable to accommodate, this difficulty is accentuated for near vision ('grasping space' and 'instrumental grasping space', as opposed to 'near-distant' and 'far-distant action space' as defined by Grüsser, 1982). Restriction of the accommodation range with blurred vision in the grasping space occurs in normal subjects older than 40 years due to presbyopia. Internal ophthalmoplegia due to lesions of the oculomotor nerve or Adie's syndrome will cause similar problems in younger patients.

Finally, as noted by Adler in 1941, 'individuals who wear strong lenses for the first time, particularly after cataract operations, also suffer from the strong prismatic effect produced from looking through the peripheral parts of the lens' and, according to our posturographic measurements, exhibit an increased body sway similar to those with bifocal or trifocal glasses. In patients with acute abnormalities of refraction, as well as with acquired disturbances of ocular motility, head and eye exercises may promote sensory rearrangements with a subsequent diminution in their perceptual and postural symptoms.

Central versus Peripheral Retina (*Experiment 2*)

This experiment is concerned with the question of the differential involvement of the central and peripheral visual fields in postural stabilization. The dominance of a small central visual field in terms of visual acuity may be counterbalanced by the wide angle motion sensitivity of the paracentral and more peripheral retinal areas, which subserve perception of self-motion relative to the surroundings.

Using optokinetic patterns of equal area, it was demonstrated by Brandt *et al.* (1973) that the peripheral retina dominates visually-induced vection, whereas central vision (central visual field up to 20 to 30 deg in diameter) dominates pattern recognition and egocentric object-motion detection. This led us to the question as to whether the mechanism of visual stabilization of posture is linked to the perception of self-motion.

Method. Field defects were simulated in 21 subjects (mean age 25 ± 6.9 years) with the aid of a cover-plate attached to a helmet. Different areas of the visual field were covered as marked at the bottom of fig. 2. A is the standard condition with both eyes open. Conditions B–G involve monocular vision. B represents body sway with one eye open and C a full monocular visual field with exclusion of the fovea. Condition D excludes the central 30 deg with its direct counterpart in E. The 30 deg field in F is similar to E except for its right paracentral location (fixation at the left border). In condition G the whole visual field is covered except for the fovea.

Results. The results point towards a large redundancy of the different parts of the visual field in reducing body sway. Inclusion or exclusion of the fovea itself inside a larger stimulus field (B *vs* C) has almost no differential effect, but exclusive stimulation of the fovea in an otherwise dark field results in a moderate but significant reduction of lateral body sway (G *vs* H). A central field 30 deg in diameter reduces lateral body sway less effectively than does the peripheral field in which the central area of 30 deg in diameter is masked (E *vs* D). The same holds for fore-aft body sway, where this relation is less prominent. A unilateral field with an area of 30 deg placed in the right hemifield adjacent to the fovea exhibits a significantly smaller contribution to standing performance for both fore-aft and lateral sway as does a central field of equal size (E *vs* F).

Comment and clinical relevance. Motion sensitivity declines towards the periphery. Regan and Beverley (1983) found a linear increase in detection threshold for lateral displacement (in-phase movement of the target corners) for target sizes of 0.5, 1 and 2 deg between 4 (threshold 2 min of arc) and 24 deg eccentricity (10 min of arc). Fore-aft displacement (change in size) of the same targets had about the same sensitivity at 4 deg eccentricity (2 min of arc), with a steeper nonlinear threshold increase with an eccentricity that was most accentuated for the smallest 0.5 deg target. Detection of movement of single horizontal lines is not different from detection of movement of two-dimensional figures (ellipses) of equal diameter (Probst *et al.*, 1984). The increase in motion threshold towards the periphery is proportional to the cortical magnification factor (Johnston and Wright, 1983). Due to this decrement in motion detection sensitivity, the peripheral retina is not capable of the fine postural adjustment of the foveal region.

This was confirmed by our and previous results (Straube *et al.*, 1983) that areas of the central retina of equal size (fig. 2, E and F) stabilize better than peripheral areas. These results point towards a fundamental difference from optokinetically induced circular vection, where a dominance of the periphery can be obtained under comparable conditions of stimulation whereas the fovea and parafoveal regions mainly subserve object-motion perception and pattern recognition (*see* Dichgans and Brandt, 1978). We conclude that visual stabilization of posture is different from circular vection such that the functional division of 'focal and ambient' vision (Leibowitz *et al.*, 1982) does not hold for stabilization of posture. Although we were able in some subjects to induce perception of self-motion with pure foveal stimulation by very slowly moving foveal targets (unpublished experiments), it is generally accepted that the fovea does not contribute significantly to circular vection. The question of whether or not perception of self-motion is a common basis for vection and visual control of posture is still open. Earlier observations with

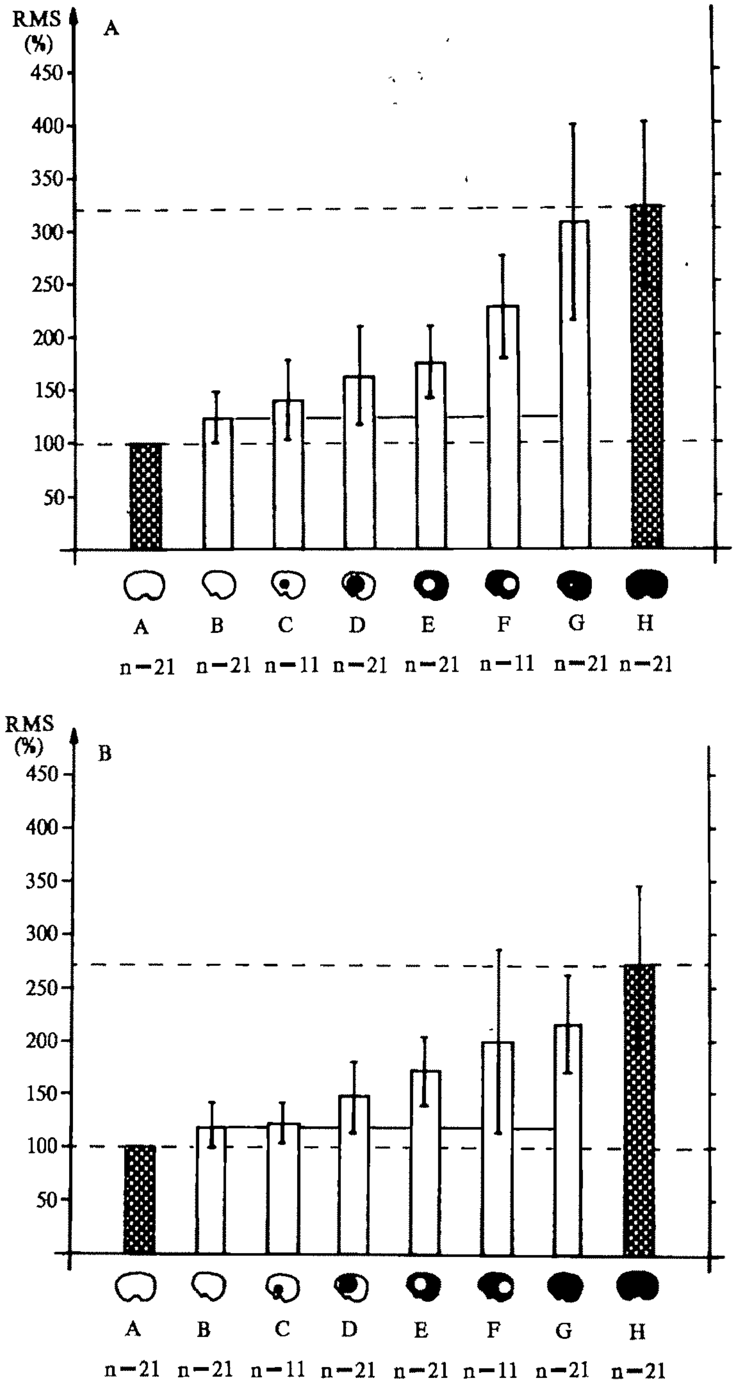

FIG. 2. Influence of central *versus* peripheral parts of the visual field on fore-aft (A) and lateral (B) body sway. Condition A represents the reference value with both eyes open, B its right eye monocular counterpart, C exclusion of the fovea (2 deg), D exclusion of the central 30 deg, E influence of the central 30 deg, F influence of a right paramedian 30 deg field, G influence of foveal vision, H body sway with closed eyes. Postural control increases with increasing area of the visual field, with equal areas of 30 deg diameter, the central visual field dominates over the periphery. The fovea, if stimulated alone, exhibits a considerable contribution to lateral but not to fore-aft sway.

optokinetic destablization of balance by use of a tilting room (Kapteyn *et al.*, 1979) revealed a measurable optokinetic destabilization even with minimal illumination levels when motion was not perceived. Under these circumstances a dissociation between motion perception and visuospinal postural regulation must be assumed.

If the single stabilizing effects of the central 30 deg field and the peripheral field (without the central 30 deg) are summated mathematically, then the calculated theoretical stabilization exceeds the real capability of the visual system. The visual field provides enough redundancy for compensation of small 'scotomas' in fine postural tuning. This explains why 100 per cent balance performance can be seen with slightly reduced visual fields or with exclusion of the fovea within the whole field although the fovea, if stimulated alone, provides a powerful contribution. The redundancy of different field areas corresponds well with a report on patients (Meienberg, 1981) where sparing of the monocular temporal crescent in homonymous hemianopia never led to any severe disability in gross orientation from their visual field deficits. The reduced capability of postural control in patients with field defects becomes particularly evident on neurological examination when tandem walking or on a rail, or when balancing on one foot. Quantitative studies on balance performance in patients with different sized scotomas at different eccentricities, however, are lacking.

Visual Stabilization in the Dark (Experiment 3)

At night visual information for postural control is usually provided by a scotopic visual scene with only some illuminated areas or single objects. This experiment is concerned with the relative influence of the number of stationary illuminated contrasts within the dark visual field as well as their location on the retina. More information on relative body movement in space is likely to be obtained from several structures in the visual space as compared with a single one.

Method. Ten subjects (mean age 26.6±4.5 years) were employed in this series. We placed 5 light-emitting diodes (LEDs) 50 cm in front of each subject in an otherwise darkened room. The 5 LEDs formed a cross with one central target in the fixation line and the 4 others 20 cm laterally on both sides, and vertically above and below the central one. The five different stimulation conditions are indicated at the top of fig. 3. Either the upper or central LEDs, or both, are illuminated, or the 4 peripheral diodes, or all 5 in the last condition.

Results. The mean fore-aft body sway with eyes closed is reduced by about one-third of the difference between the eyes closed and the standard condition with eyes open with one central LED subserving visual stabilization. Additional presentation of a second upper target alone does not exert a significant influence. All 5, or just the 4 peripheral LEDs, however, cause a further reduction in body sway, one-third less than with the whole-field reference stimulation.

The central LED seems to be of importance only for lateral sway reduction. Inclusion of the central LED causes a further reduction of almost 50 per cent in lateral body sway, in contrast to fore-aft sway, while fore-aft and lateral body sway in conditions 1 and 4, where the central LED is not illuminated, are reduced to an

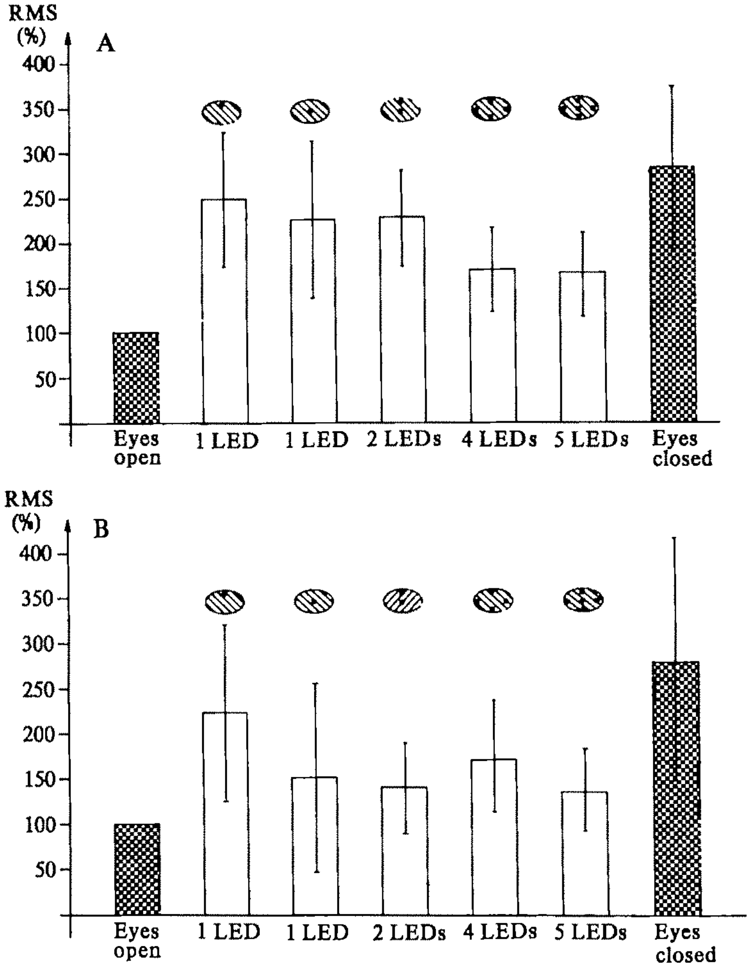

FIG. 3. Stabilizing effects of single visual targets in darkness provided by light-emitting diodes (LEDs) placed at a distance of 50 cm in front of the eyes. A and B as in fig 1. One single stationary light is sufficient significantly to improve at least lateral postural sway, an effect which is increased for both sways with additional targets. In the first condition only the upper, in second the central, in third both upper and central LEDs, in fourth all 4 peripheral and in fifth condition all 5 LEDs are switched on in an otherwise dark room.

equal extent. These findings again provide evidence for a contribution of the foveal region in detecting and correcting lateral body sway shifts, particularly for small targets. With respect to fore-aft sway, change in size seems to be more powerful than change in disparity, since movement of the foveal target is mainly detected by change in disparity while change in size information is mainly provided by the peripheral targets (*see* General Discussion).

In a control experiment no difference between RMS values in a dark room with eyes closed, eyes open and fixation of two LEDs coupled with head movements (negative feed-back) could be detected.

Comment. One central target in an otherwise dark environment provides a reduction in lateral sway activity with the eyes closed from 280 to 150 per cent. The addition of 4 peripheral targets reduces sway only down to 130 per cent (100% = standard condition with full illumination). This again supports the importance of the foveal contribution in detection and correction of lateral body sway. In control experiments with a target by the fovea, fixated combined with head movements in the dark and with the eyes open in the dark, no evidence for negative feed-back was found, since the resulting instability was identical with the values obtained with closed eyes.

Retinal Slip versus Retinal Dislocation (*Experiment 4*)

Eye movements consist either of saccades or smooth pursuit. While continuous information inflow is provided during smooth pursuit movements, during saccades suppression of motion perception masks the visual input. Although a deterioration of balance during saccades might be expected, saccadic eye movements did not affect balance in the experimental conditions employed by White *et al.* (1980). A continuous information inflow seems not to be a necessary visual condition for maintaining balance.

The flicker light Experiment 4 was designed in order to evaluate the differential effects of continuous *versus* discrete visual inputs, which correspond respectively to detection of retinal slip and retinal dislocation of viewed targets.

Method. Ten subjects (mean age 26.7±3.9 years) were placed 1 m in front of a random dot background screen. Surround illumination was flashed stroboscopically with flicker frequencies between 1 and 32 Hz (*see* fig. 4). The light intensity of the stroboscope measured at the flicker fusion frequency of 60 Hz was 30 cd/m^2.

Results. With flicker frequencies of 16 and 32 Hz, body sway did not differ significantly as compared with uniform room illumination (fig. 4). A flicker frequency of 8 Hz, however, causes an increase in body sway of about 30 per cent, whereas all frequencies tested below 8 Hz (1, 2, 4 Hz) caused a common increase of instability of about 60 per cent. No difference between fore-aft and lateral body

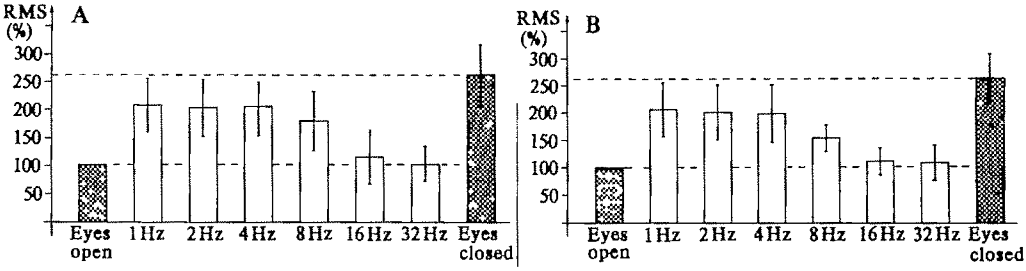

FIG. 4. Differential effects of stroboscopic illumination on fore-aft (A) and lateral (B) body sway by use of flicker frequencies between 1 Hz and 32 Hz With purely retinal displacement of the visual scene at flicker frequencies between 1 and 4 Hz, a partial but significant reduction in sway is provided, which gradually improves with increasing frequencies when continuous motion perception becomes involved.

sway can be detected except at 8 Hz, at which frequency fore-aft sway was significantly higher than lateral sway.

Comment and clinical relevance. The physiological implication of these results is that continuous motion of the retinal image is the most effective stimulus in postural stabilization, but is not an essential precondition. With purely sequential retinal displacements of the visual scene due to flicker illumination, a partial but significant visual stabilization of posture is preserved, which surprisingly does not depend on flicker frequency between 1 to 4 Hz (fig. 4). As soon as continuous motion perception rather than stepwise changes in retinal location became involved (with strobe frequencies higher than 4 Hz), visual stabilization gradually improved with increasing frequencies.

Fig. 4 indicates three ranges of visual input rate with different influence on posture: 1–4 Hz, 4–16 Hz, 16 Hz to flicker fusion frequency. At frequencies between 1 and 4 Hz a constant decrement of balance of about 60 per cent compared with the 'eyes-open' condition can be seen. These data contradict earlier results by Amblard and Crémieux (1976), who found that visual stabilization was absent at strobe frequencies of up to 6 Hz. In more recent work they also described 'two separated visual mechanisms for the control of body balance in man' which depend on flicker frequency (Crémieux *et al.*, 1984). Kapteyn *et al.* (1979) described a quite constant difference in sway amplitude between 1 and 5 Hz compared with steady illumination. They used a tilting room which induced an optokinetic destabilization.

The flicker frequency of 8 Hz introduces a further significant reduction of balance compared with frequencies below 4 Hz, with a saturation at frequencies higher than 16 Hz. This frequency range is somewhat intermediate between the *Gestalt* fusion frequency of about 4 to 6 Hz and the flicker fusion frequency between about 20 Hz to 80 Hz depending on the illumination level. It might be speculated that the continuous perception of self-motion in space is less complex than *Gestalt* perception, but more complex than the evaluation of flicker fusion.

This may be related to technical considerations given by the 'Nyquist theorem'. Normal subjects as well as patients with ataxia frequently oscillate with a 3 to 4 Hz peak depicted by Fourier analysis. According to the Nyquist theorem, signal points have to be sampled at twice the upper frequency limit assessed by Fourier analysis. By analogy, the human CNS requires visual information of about 6–8/s to be able to control visually the 3 to 4 Hz sway peak.

If, as suggested by Ullman (1979), we need to view three different aspects to perceive structure from motion, we have to multiply this lower frequency by a factor of three for full visual stabilization. It could be speculated that this might be the reason for the frequency of the higher full stabilization range starting at about 16 Hz compared with the lower frequency range of about 6 Hz for motor commands. The smaller reduction of fore-aft sway compared with lateral sway with 8 Hz flicker supports the view that fore-aft movement detection is more complex and requires more information than lateral movement detection. It was demonstrated by Nashner and Berthoz (1978) and by Vidal *et al.* (1982) that the motor system is in fact able to follow frequencies up to about 6 Hz, since the visuomotor reaction time was determined with a delay of 100 ms for the onset of EMG activity and a corresponding peak at about 150 to 200 ms in the gastrocnemius muscle.

With respect to clinical relevance, acquired ocular oscillations may (1) impair the mechanism of continuous motion perception and (2), due to oscillopsia, cause misleading motion input with a deleterious influence on posture. Involuntary ocular oscillations such as acquired pendular nystagmus, spasmus nutans, superior oblique myokymia or downbeat nystagmus, are not associated with an appropriate efference copy signal and therefore cause oscillopsia and postural imbalance even in the absence of voluntary head and eye movements. The disturbance of spatial localization due to oscillopsia is not restricted to the fovea, but involves the entire visual field and therefore affects the two modes of visual processing, 'focal' and 'ambient' (Brandt *et al.*, 1982; Wist *et al.*, 1983). In downbeat nystagmus the patient's pathological postural sway depends on the direction of gaze becoming accentuated with increasing amplitude of nystagmus (fig. 5).

In the particular example of the 'downbeat nystagmus vertigo syndrome', pathophysiologically ataxia is secondary to a combination both of a vestibulocerebellar ataxia with a tendency to fall backwards (in compensation for the forward vertigo produced by the lesion) and reduced visual stabilization because of the nystagmus (Büchele *et al.*, 1983).

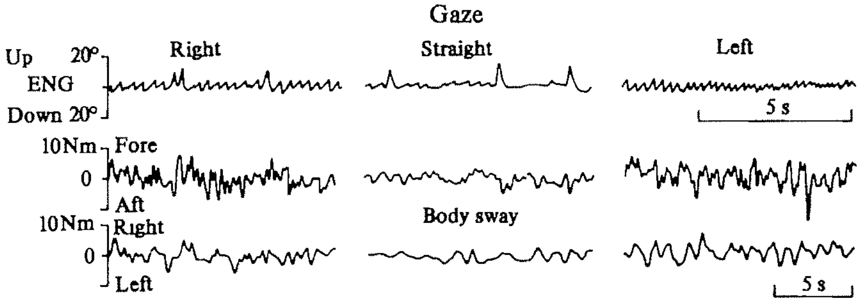

FIG. 5. Original recordings of vertical electronystagmography (ENG) and simultaneous fore-aft and lateral sway in a patient with a downbeat nystagmus syndrome. The pathological postural sway is also dependent on the direction of gaze because of reduced visual stabilization owing to the nystagmus and oscillopsia.

Near Vision and Eye-object Distance (Experiment 5)

Visual stabilization in 'grasping space' involves eye-object distance as a critical physical stimulus characteristic. For simple geometric reasons the relative retinal shift of a viewed scene is greater the nearer the objects are to the eyes. The question is whether or not the gradual approach of a subject towards a stationary surround is reflected in a gradual improvement of postural balance within the grasping space. Such a relationship was demonstrated by earlier observations by Bles *et al.* (1980) who were interested in gross differences between near and far vision.

Convergence as well as accommodation may play a significant role in the regulation of balance. Both produce double vision of visual targets before or beyond the plane of fixation, with a corresponding alteration in visual acuity.

Method. The following three sets of experiment were designed to differentiate between the effects of eye-object distance, visual acuity, accommodation and convergence.

(a) The 12 subjects (mean age 22.5 ± 4.5 years) were placed at different distances from a flat structured background. Stepwise changes of background distance were chosen in units of 2 accommodation dioptres starting with 50 cm (2 dpt), 25 cm (4 dpt), 16.6 cm (6 dpt), 12.5 cm (8 dpt) and 10 cm (10 dpt).

(b) The subjects were placed at a distance of 100 cm in front of the background. A stationary fixation target varying in diameter in order to correct for the distance and to cover the 2 deg fovea, was placed in front of the subjects' eyes at distances between 50 and 10 cm, as before. Subjects were instructed to fixate the target, although this was difficult to maintain for the total test time (1 min) at shorter distances (such as 10 cm).

(c) The same experimental arrangement was used, except that the fixation targets were attached to a helmet. As the fixation point was coupled with head movement, it did not provide information about a stationary surround. Foveal vision therefore did not provide usable information concerning motion.

Results. The results obtained are as follows (*see* fig. 6).

(a) A further gradual improvement in balance down to about 60 per cent of standard body sway with the eyes open and 100 cm distance was seen for both fore-aft and lateral body sway with decreasing eye-background distances down to 12.5 cm (8 dpt). The relationship between lateral sway activity Y_l, fore-aft sway activity Y_{fa} (percentage RMS values) and distance D to the wall (cm) is best described by linear regression equations (Eq. 2a, b) with correlation coefficients of 0.98 and 0.93 respectively:

$$Y_l = 56.9 + 0.44 * D \tag{2a}$$

$$Y_{fa} = 60 + 0.42 * D \tag{2b}$$

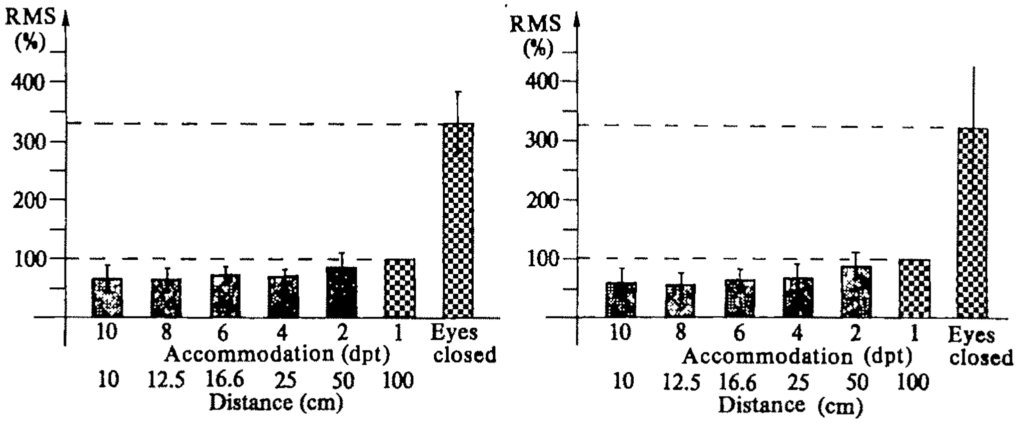

FIG. 6A. Influence of the distance between eyes and the stationary flat background on posture stability for fore-aft (*left*) and lateral (*right*) body sway for distances between 10 and 100 cm. The linearly decreasing body sway activity with decreasing eye-object distance corresponds to the net retinal displacement of the viewed stationary background due to head motion.

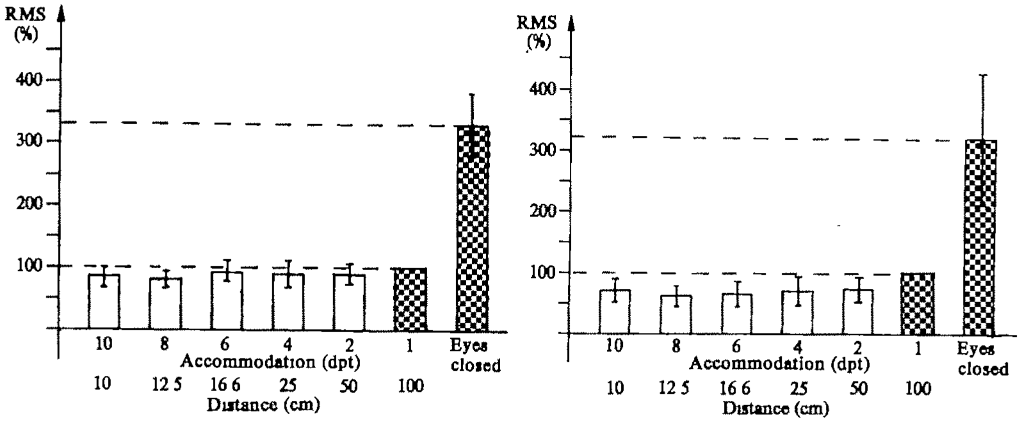

FIG. 6B. Influence of foveal vision (2 deg target) on posture. This stationary foveal target varied between 10 cm and 1 m, similar to the background distances in fig. 6A. In this experiment the background was kept constant at 1 m distance. The reduction in sway is similar in amplitude as compared with the effect of the whole field stimulus in Experiment 6(a). Fore-aft (*left*) and lateral (*right*) body sway.

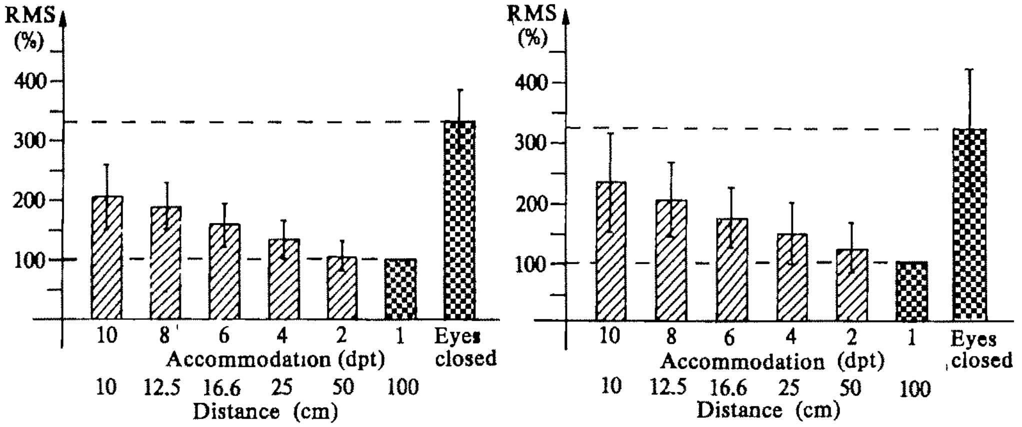

FIG. 6C. Control experiment for fig. 6B, with the 2 deg target attached to a helmet. Thus the foveal target provides no information on body sway and, depending on the distance, the stationary background appears increasingly blurred for eye-target distances between 50 and 10 cm. Fore-aft (*left*) and lateral (*right*) body sway. The data correspond to the effect of diminished visual acuity in fig. 1.

(b) The ability of foveal vision to reduce fore-aft sway less than lateral sway (fig. 3), as already demonstrated was again evident (fig. 6B). Here the 2 deg target fixated by the fovea caused a reduction of instability to about 20 per cent (fore-aft sway) and 40 per cent (lateral sway) when brought closer to the eyes in front of the background at 100 cm. The relationship between distance (D) to the foveation target and RMS values was poor, with a correlation coefficient of 0.6.

(c) When the foveal target was coupled with head movements, an increasing instability was seen with decreasing fixation distance. This simultaneously brought the background out of focus. The relationship for lateral (Eq. 3a) and fore-aft (Eq. 3b) body sway and target distance can be described by semilogarithmic equations (correlation coefficients 0.94 and 0.97):

$$Y_l = 375.8 - 67 * \ln(D) \quad (3a)$$

$$Y_{fa} = 340.6 - 61.2 * \ln(D) \quad (3b)$$

The effect obtained with monocular fixation was not as pronounced as with binocular fixation and is not demonstrated.

Comment. The general improvement in postural sway while fixating close visual targets in the grasping space can be related to better resolution in the detection of relative motion of head sway because of the greater retinal shifts. The slight increase of postural instability at a distance of 10 cm as compared with 12.5 cm, however, must be attributed to increasing difficulties in accommodation. Thus with very close distances between eye and background the 'geometric postural effect' of greater retinal shifts is counterbalanced by the negative effect of accommodation difficulties, with consequent decrements in visual acuity. The results of Experiments 5a–c reflect common differences for lateral as compared with fore-aft body sway, the physiological basis for which will be considered in relation to the data on visual acuity in the General Discussion.

GENERAL DISCUSSION

Fore-aft Versus Lateral Body Sway

With experimentally altered visual acuities between 0.6 and 0.01 a stabilization of lateral sway can be clearly seen with a visual acuity of 0.01, which is absent in the fore-aft sway component. The decreasing stability already apparent with a reduction in visual acuity to 0.6 (fig. 1) suggests that the normal high (foveal and/or peripheral) resolution is used for correction of balance.

Although both lateral and fore-aft body sway increase with reduced visual function, different geometric aspects of the detectability of relative eye-object motion and the mode of afferent/efferent motion perception must account for the significantly steeper increase in fore-aft sway, as evident by comparing Eqs 1a and b.

During fixation of a stationary target, lateral head displacement is mainly monitored by use of information derived from following eye movements, the so-called 'efferent movement detection'. Fore-aft sway, however, can be detected by two mechanisms: change in disparity and change in target size (Regan and Beverley, 1979). Change in disparity is a purely binocular mechanism with the greatest sensitivity at shorter distances, it involves 'efferent motion perception' for vergence movements. Changing size of a visual target, from a change in eye-object distance, is a purely sensory mechanism. Particularly for large distant stimuli, its sensitivity is superior for detection of movement in depth as compared with change in disparity, since the change in size is proportional to target size. Change in disparity depends mainly on the interocular distance, which is comparatively small for large target distances.

As stated by Regan and Beverley (1979), 'changing-size' would be 76 times more effective than 'changing-disparity' as a stimulus for motion in depth for a landing airplane with angular width of 2.72 deg of the runway. In contrast 'changing-disparity' would be 72 times more effective than 'changing'-size' as a stimulus for motion in depth in case of a fly moving at 50 cm distance towards a subject. The authors added several other aspects which influence object motion perception in depth. Loss of binocular vision is less important for short inspection times. Visual sensitivity to low velocities and visual sensitivity to the motion-in-depth of wider objects are less affected by the loss of binocular vision except at very short distances. Binocular thresholds are up to about 1.4 times lower than monocular thresholds with 'changing-size' stimulation. Large interindividual differences (up to 80 : 1) exist in the relative effectiveness of 'changing-size' and 'changing-disparity' in producing a sensation of motion in depth.

With free upright stance the angle α_1 of the 'relative' lateral retinal displacement of a viewed stationary target is dependent upon the eye-target distance (D) and the amplitude of the lateral head shift (ΔD, units in metres) as defined by Eq. (4):

$$\alpha_1 = \arctan(\Delta \mathrm{D}/\mathrm{D}) \tag{4}$$

As already mentioned, owing to the closed-loop condition with following eye movements, this angle is mainly monitored by 'efferent' rather than 'afferent' motion perception. Accurate evaluation of the adequate compensatory motor command to maintain posture requires knowledge of the target distance D, since with a given angle α_1, lateral head shift ΔD is proportional to D (Eq. 2). Thus adjustment of lateral sway correction depends partly on depth perception. Hindrance of depth perception may be one of the reasons why, in contrast to simple visual blur in Experiment 1, blurring of the stationary background by fixation of a nearby target, coupled to the head movements, affects lateral more than fore-aft sway (fig. 6C). It is interesting to note that recently units with the adequate sensitivity for the detection of lateral displacement have been described in the middle temporal visual areas of the macaque monkey (Maunsell and Van Essen, 1983). About two-thirds of the cells tested showed pronounced frontoparallel movement sensitivity at a fixed disparity, but no unit was found to be truly selective for motion in depth.

The geometric basis of change in disparity and change in size due to head sway is more complex (detailed assessment in Regan and Beverley, 1979). The angle Θ which characterizes the change in size may be evaluated by aid of Eq. (5) (D = target distance, ΔD = fore-aft shift, S = target width, I = interocular distance (all units in m, for example)):

$$\Theta_s = \arctan((\mathrm{I}/2+\mathrm{S}/2)/(\mathrm{D}-\Delta \mathrm{D})) * \arctan((\mathrm{I}/2-\mathrm{S}/2)/(\mathrm{D}-\Delta \mathrm{D})). \tag{5}$$

Two angles Θ_s have to be calculated first by inserting ΔD = 0, and secondly the proposed fore-aft shift ΔD. The angular increase or decrease in size is defined by the difference of both absolute angles. When calculating change in disparity the same procedure is necessary; however, the minus sign marked with −* in Eq. (5) has to be replaced by a plus sign. These calculations reflect the situation when standing in front of a flat frontoparallel background. Matters are complicated in a surround with a three dimensional structure with nearby objects in the peripheral visual field which, with fore-aft sway, move across the peripheral retina more probably as indicated in Eq. (4) for lateral sway. If the object is located to either side with an angle of 90 deg to the fixation line, Eq. (5) is no longer defined since its distance D would be zero and its size S would be infinite. This geometric problem has been avoided in our experiments with the flat-structured surround. Because of the decline in motion sensitivity of the peripheral retina, its contribution to balance is probably low as compared with the foveal contribution to reduction of lateral sway.

Since low frequencies (< 1 to 5 Hz) mainly constitute physiological postural sway, the data of Scobey and Johnson (1981) may also serve as a basis for the sensitivity of self-motion detection in postural sway. The authors measured the threshold sensitivity for an oscillatory object movement of a single line within this frequency range. The threshold for detection of object oscillation was 2 min/arc for frequencies between 3 to 10 Hz, which increased to about 5 min/arc at a frequency of 1 Hz. Lateral angular displacements of 2 min/arc on the foveal retina may therefore represent the highest visual resolution in the evaluation of normal body sway.

Depending on eye-target distance, different magnitudes of lateral and fore-aft sway are necessary to cause a net lateral retinal displacement of two min of arc, as summarized in the Table (fore-aft sway evaluated by a combination of change in disparity and change in size; assumed target size 5 cm). This shows that there is a linear correlation between eye-target distance for lateral sway according to Eq. 1, but a steep nonlinear increase of necessary fore-aft head sway with increasing target distance, especially beyond the grasping space.

TABLE. DETECTION OF MINIMAL BODY SWAY AMPLITUDE IN RELATION TO EYE-OBJECT DISTANCE

Distance	*Lateral sway*	*Fore-aft sway*
10 cm	0.0056 cm	0.005 cm
50 cm	0.028 cm	0.092 cm
1 m	0.056 cm	0.37 cm
100 m	5.6 cm	37.3 m

Retinal displacement of 2 min/arc has also been reported to be a threshold condition for postural instability in situations inducing height vertigo, beginning at an absolute height of 3 to 4 m (Bles *et al.*, 1980; Brandt *et al.*, 1980). With a severe reduction in VA, as in patients with uncorrected cataracts, a comparable imbalance is induced at the normal eye-foot distance of 1.50 m, since at this distance normal head oscillations cannot be detected.

In the monocular visual field reductions in Experiment 2, change in size can be confirmed as the underlying fore-aft detection mechanism by calculating the theoretical angles for 'changing-size' and the corresponding binocular 'changing-disparity' values from Eq. 5. An average fore-aft head sway of 2 cm (Kapteyn, 1973) is assumed for ΔD. As expected, a good inverse correlation can be found between angular target change in size and RMS values, but not between change in disparity and RMS values.

In the binocular conditions of Experiment 3, fore-aft sway as compared with lateral sway is only minimally reduced by a single central target from 280 to 230 per cent, whereas all 5 targets cause a significant decrease to 170 per cent. The striking reduction in sway with a minimum of 4 targets did not depend on the inclusion of the foveal target in contrast to lateral sway. Again this decrease corresponds closely to the calculated values for change in size; the particular experimental conditions cause a relatively small, noncorresponding change in disparity.

This critical number 4 for perception of change in size may be related to the mechanism for the detection of structure from motion. To perceive a three-dimensional structure in space, three different aspects of four noncoplanar points suffice to determine their three-dimensional structure (Ullman, 1979). This is not restricted to apparent motion: in continuous motion the visual input which counts as 'three aspects' depends solely on the resolution of the underlying systems measuring the position changes in time. Our experimental condition with 4 or 5 targets in the dark may depend on a similar mechanism, which infers body position relative to stationary targets from figural change due to the motion.

The linear decrease in lateral body sway in Experiment 5, which is evident in the grasping space as the target approaches the eye, corresponds well to the mechanism for the detection of lateral displacement discussed in Eq. 4. For fore-aft sway, the lower correlation coefficient for the linear regression (0.93) reflects the more complex geometric aspects expressed in Eq. 5.

Sway reduction with fixation of the target foveal 2 deg in fig. 6B is comparable in size to the reduction seen with fixation of the whole field stimulus in fig. 6A, although there is no comparable linear decrease with decreasing distance. Since in Experiments 5a and b, balance improved with closer target distance, accommodation and convergence themselves do not cause a deterioration of balance. The maximal possible reduction of sway to 60 per cent with a close whole field stimulus indicates a lower limit of body sway mainly due to mechanical mechanisms.

The effect of imbalance in Experiment 5c can be related to blurring of the background during fixation of the foveal target. The semilogarithmic increase in sway activity with decreasing head-coupled target distance in fig. 6C reflects quite well the semilogarithmic relationship between visual acuity and dioptric blurring of an image (cf. Experiment 1). Increased blurring of the stationary background with decreasing target distance accounts for the functional decrease in VA and subsequent decrease in balance. So far, the effects in Experiment 5c are in good agreement with the data of fig. 1. There is however an interesting difference. In contrast to simple optical blurring in Experiment 1, fore-aft sway in Experiment 5c is less affected than lateral sway, as may be seen in the steeper increase of the function (5a) compared with (5b). The physiological correlate concerns the difference between the perception of afferent and efferent motion. Efferent motion perception will be impeded in patients with cerebellar lesions and saccadic eye movements and in patients with ophthalmoplegia from varies causes (e.g. Graves' disease, 'ophthalmoplegia plus', progressive supranuclear palsy). In contrast to Experiment 1, fixation of the head-coupled target largely prevents efferent motion perception of the stationary background in Experiment 5c. Head displacement has to be evaluated by afferent motion perception, which seems to have a lower sensitivity for the detection of lateral sway as compared with fore-aft sway. The two different experimental conditions of Experiments 1 and 5 may thus serve as a model for the analysis of the different aspects the perception of afferent and efferent motion.

ACKNOWLEDGEMENTS

We are grateful to Dr J. A. Büttner-Ennever for helpful comments on the manuscript. This work was supported by Deutsche Forschungsgemeinschaft, Br 639/4-4 'Bewegungskrankheit'.

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(*Received January 19, 1984. Revised May 11, 1984*)

Brain (1984), 107, 1165-1177

A NEW MITOCHONDRIAL MYOPATHY

BIOCHEMICAL STUDIES REVEALING A DEFICIENCY IN THE CYTOCHROME b-c_1 COMPLEX (COMPLEX III) OF THE RESPIRATORY CHAIN

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SUMMARY

A 20-year-old Chilean girl presented with lifelong ptosis and fatiguable weakness which was initially thought to be due to a congenital myasthenic syndrome. Studies of an intercostal muscle biopsy showed normal endplate morphology, abundant acetylcholinesterase activity and a normal number of junctional acetylcholine receptors as determined by radiochemical assay, but a high proportion of the muscle fibres contained large peripheral aggregations of abnormal mitochondria. Biochemical investigation of mitochondria isolated from the vastus lateralis muscle demonstrated a hitherto unreported respiratory chain deficiency localized to complex III.

INTRODUCTION

Although the mitochondrion has been known for over a century, it is only in the last three decades that the main details of its function and biosynthesis have been elucidated (Ernster and Schatz, 1981). One of its major activities is the synthesis of ATP from ADP and P_i by oxidative phosphorylation, a pathway which utilizes reducing potential generated by several oxidative systems, in particular the citric acid cycle (Lehninger, 1982). The mitochondrion also possesses its own DNA which is now known to code for several polypeptide components of the respiratory enzyme complexes within the inner membrane (Tzagoloff *et al.*, 1979; Anderson *et al.*, 1981; Slonimski *et al.*, 1982; Grivell, 1983).

Since the first description of a biochemically proven abnormality of oxidative phosphorylation in man (Luft *et al.*, 1962), there has been a growing literature on mitochondrial defects in human skeletal muscle (DiMauro, 1979; Land and Clark, 1979; Carafoli and Roman, 1980; Morgan-Hughes, 1982*a*, *b*). Although disorders of this type vary widely in their clinical expression (Boustany *et al.*, 1983; DiMauro *et al.*, 1983; Morgan-Hughes, 1983), many cases have presented with weakness and severe exercise intolerance (Morgan-Hughes *et al.*, 1977, 1979; Land *et al.*, 1981;

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Darley-Usmar *et al.*, 1983; Morgan-Hughes *et al.*, 1984*a*), reminiscent of that seen in congenital myasthenic syndromes (Engel, 1980). It was because of lifelong and striking fatiguable weakness, ptosis and an apparently normal muscle biopsy report from elsewhere, that the patient described in this paper was initially thought to be suffering from a congenital defect of neuromuscular transmission.

CASE REPORT

M.A. (National Hospital No. B24544), a 20-year-old Chilean girl, was admitted to the National Hospital in June 1982 for investigation of weakness and exercise intolerance dating back to early childhood. There was no family history of neuromuscular disease and no parental consanguinity. Three sisters and a brother were said to be well. Her birth and early development were normal. At the age of 5 years it was noted that she tired easily when walking and was unable to hurry. In attempting to keep up with other children she quickly became breathless and complained of weakness and stiffness in her legs. Over the years her exercise intolerance had fluctuated in severity but had shown little tendency to progress. When first seen at the age of 19 years she was only able to walk approximately 400 yards on the flat before having to rest and had difficulty in climbing more than one flight of stairs. She had not suffered muscle pain or cramp and there was no history of pigmenturia.

On examination she had mild bilateral ptosis which was not fatiguable. Ocular movements were normal. There was minimal weakness of eye closure and fatiguable weakness of the sternomastoid muscles. Muscle bulk was normal in the limbs but there was mild diffuse weakness which became more marked during sustained effort against resistance. She was unable to sit up from a supine position without using her arms. The reflexes were sluggish in the upper limbs but normal in the legs, and the plantar responses were flexor. General examination was normal with a blood pressure of 110/70.

A routine blood count, sedimentation rate, serum electrolytes, blood urea, blood sugar, liver function tests, T_4 and syphilitic serology were normal. The serum CK was normal (25 IU/l) An autoantibody screen was negative and acetylcholine receptor (AChR) antibodies were not detected in the blood. An ECG, echocardiogram and chest x-ray were normal. EMG studies showed myopathic potentials with normal motor and sensory conduction. Tests of neuromuscular transmission including single fibre EMG were normal. There was no response to intravenous edrophonium.

During a standard 10 min exercise test on a bicycle ergometer (Morgan-Hughes *et al.*, 1977) the lactate level in venous blood rose from 0.5 to 4.5 mmol/l and was still raised at 2.5 mmol/l 1 h later.

Special Investigations

Muscle biopsies. Samples were obtained under light general anaesthesia from the left ninth external intercostal muscle (for junctional AChR assay) and from the left vastus lateralis muscle for *in vitro* mitochondrial studies. Separate specimens from each biopsy were processed for histochemistry as described previously (Morgan-Hughes *et al.*, 1970). Cytochrome c oxidase activity was demonstrated by the method of Seligman *et al.* (1968). For electron microscopy the sample was removed at resting length and fixed in 3 per cent glutaraldehyde in 0.1 mmol/l sodium cacodylate buffer (pH 7.3) for 2 h. Specimens were postfixed in 1 per cent aqueous osmium tetroxide, dehydrated in graded concentrations of ethanol and embedded in Epon 812 epoxy resin. Thin sections were stained in a saturated solution of uranyl acetate in methanol and 1 per cent aqueous lead citrate and examined at 80 kV.

Radiochemical assay of junctional AChR. Junctional AChR were assayed on small bundles of freshly isolated external intercostal muscle fibres using 50 nmol/l monoiodinated ^{125}I-α-bungarotoxin (α-bgtx) with a specific activity of 200 Ci/mmol. The number of AChR, the K_{+1} for toxin binding and I_{50} values for acetylcholine and d-tubocurarine were determined according to methods previously described (Lecky and Morgan-Hughes, 1981; Morgan-Hughes *et al.*, 1981).

Preparation of mitochondria. Mitochondria were isolated from a sample of the left vastus lateralis muscle (8 g) by the method of Makinen and Lee (1968) as described previously (Morgan-Hughes *et al.*, 1977, 1982). The mitochondrial fraction was prepared within 50 min of the biopsy being taken. The yield was approximately 0.8 mg mitochondrial protein/g wet weight of muscle. Protein was measured by the method of Lowry *et al.* (1951) using bovine serum albumin as standard.

Respiratory and low temperature spectral studies. Oxygen uptakes were measured polarographically at 25° C with a Clark-type electrode (Morgan-Hughes *et al.*, 1977). Low temperature (77° K) spectral studies were also carried out as described previously (Morgan-Hughes *et al.*, 1977). The cytochrome contents were calculated using the extinction coefficients quoted by Wilson and Epel (1968) and an intensification factor of 7 (Wilson, 1967).

Enzyme and metabolite assay. Enzymes were measured at 25° C using an SP 8–100 recording spectrophotometer. Maximum enzyme rates were obtained by including 0.1 per cent (Fc) Triton-X-100 in the assay medium. Pyruvate dehydrogenase (EC 1.2.4.1.) and citrate synthase (EC 4.1.3.7.) were assayed as described by Morgan Hughes *et al.* (1977), NADH-ferricyanide reductase by the method of King and Howard (1967). Venous lactate was measured as described by Bergmeyer *et al.* (1974). Total muscle carnitine was assayed by the method of Marquis and Fritz (1965).

Chemicals. Enzymes and cofactors used in this study were obtained from Boehringer Corporation Ltd, Lewes, Sussex. Monoiodinated ^{125}I-α-bgtx was obtained from Amersham International. All other reagents were of analytical grade. Solutions were prepared with fresh double glass distilled water.

RESULTS

Muscle Histochemistry

The left vastus lateralis muscle contained a full complement of muscle fibres with diameters ranging from 30 to 70 μm (mean 53 μm). Many of the fibres showed typical ragged red changes with the Gomori trichrome stain and gave an intense reaction for succinate dehydrogenase (fig. 1A). In 6 nonoverlapping areas consisting of 640 fibres the proportion of ragged red fibres ranged from 24 to 73 per cent. Virtually all the fibres (99%) with increased succinate dehydrogenase activity were cytochrome oxidase negative in serial transverse sections whereas the surrounding nonragged red fibres showed a relatively normal reaction (fig. 1B). With the myofibrillar ATPase reactions, 70 per cent of the type 1 fibres and 47 per cent of type 2a fibres showed ragged red changes. Type 2b ragged red fibres were not seen but the biopsy contained only very few fibres belonging to this histochemical type (fig. 1C). Of the total fibre population, 62 per cent were type 1, 37 per cent were type 2a, and only 1 per cent were type 2b.

Essentially similar changes were seen in the external intercostal muscle but the ragged red fibres were more patchily distributed. As in the vastus lateralis, cytochrome oxidase negative fibres corresponded to those showing enhanced succinate dehydrogenase activity. The endplates were normal in size and shape and showed abundant cholinesterase activity.

Electron Microscopy

The majority of the intercostal muscle fibres examined showed conspicuous peripheral accumulations of abnormal mitochondria embedded in glycogen-rich cytoplasm (fig. 2). These organelles showed a wide range of sizes and structural

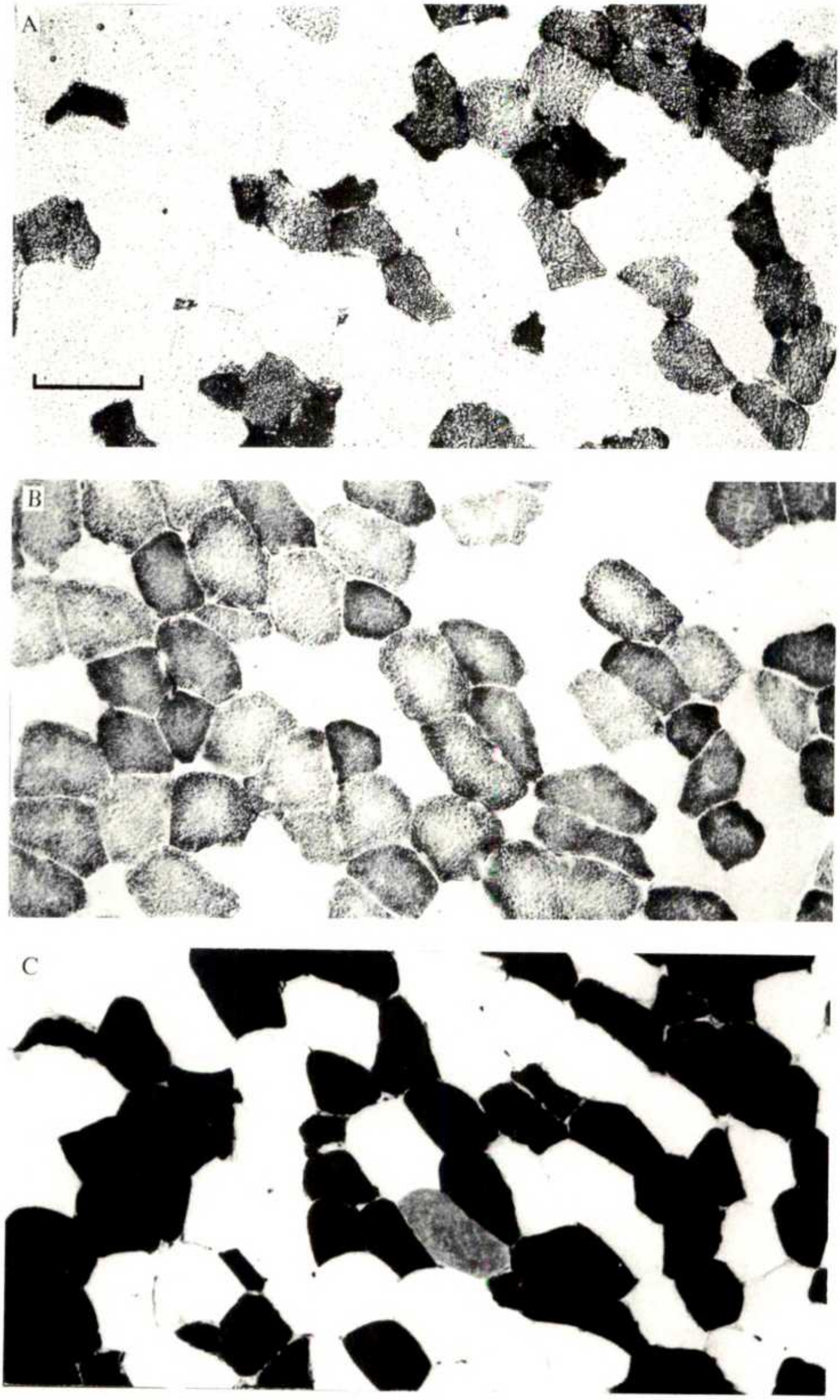

FIG. 1. Serial sections of the left vastus lateralis muscle stained for A, succinate dehydrogenase; B, cytochrome c oxidase and C, myofibrillar ATPase at pH 4.6. Note the cytochrome oxidase negative ragged red fibres and the deficiency of type 2b fibres. Bar = 100 μm.

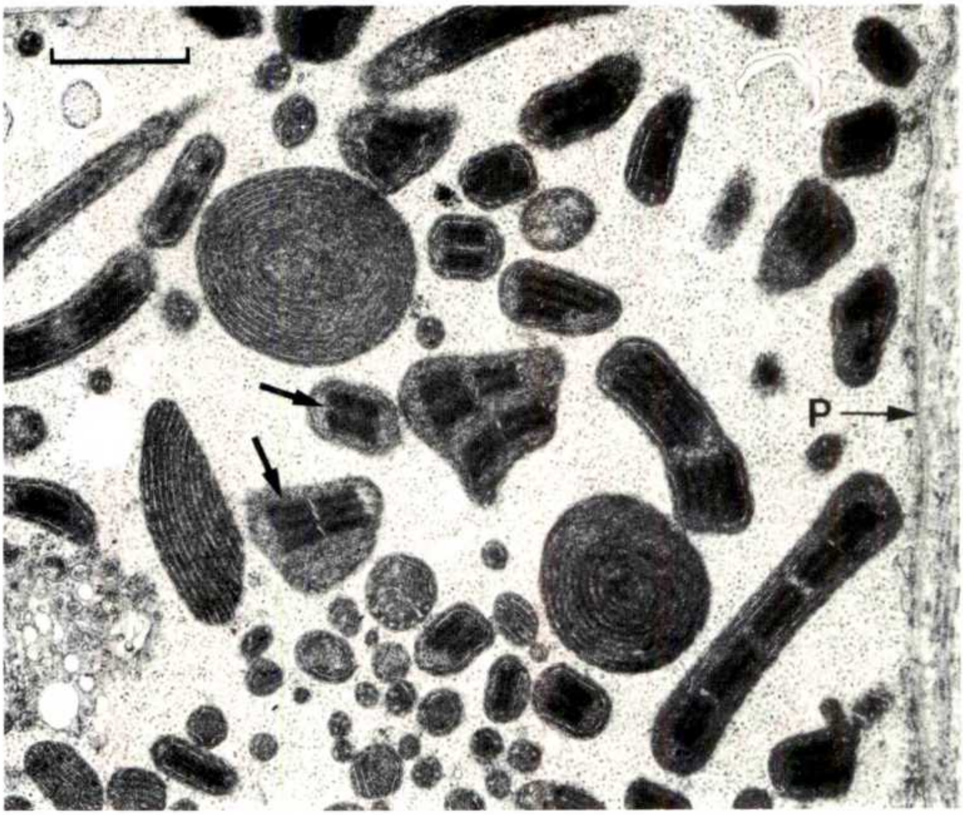

FIG. 2. Electron micrograph of the periphery of an intercostal muscle fibre to show a collection of abnormal mitochondria embedded in glycogen rich cytoplasm. P = plasma membrane. Examples of paracrystalline inclusions are arrowed. Bar = 0.5 μm.

abnormalities and included giant mitochondria with parallel or concentric cristae, central droplets of neutral or osmiophilic lipid or areas of central necrosis. Many of the smaller mitochondria also showed morphological abnormalities, of which the most common was the presence of a single circumferential crista surrounding a solid core of granular matrix. Mitochondria of all sizes contained single or multiple paracrystalline inclusions which were predominantly of the type 1 or 'parking lot' type (fig. 2). Other fibres with similar but less marked mitochondrial changes also possessed abundant glycogen-rich sarcoplasm which sometimes separated the individual myofibrils and contained occasional neutral lipid droplets. There was a moderate increase in endomysial connective tissue and the basal laminae surrounding some capillaries appeared to be slightly thickened. Two neuromuscular junctions were observed and showed no evidence of axonal or endplate pathology.

Similar changes were seen in the left vastus lateralis muscle. The large peripheral accumulations of mitochondria were contained within glycogen-rich sarcoplasm which sometimes extended between the myofibrils. Type I and type II paracrystalline inclusions were common in both large and small mitochondria. Interstitial collagen was moderately increased and the capillary basal laminae were thickened in most instances.

Junctional AChR

With 50 nmol/l ^{125}I-α-bgtx, the patient's receptors saturated at 30 attomol per endplate. Saturation values for 16 control subjects ranged from 13.4 to 31.8 attomol per endplate (mean ± SD 22.07 ± 5.46). The calculated number of toxin binding sites per endplate was 1.8×10^7 for the patient compared with a range of 0.8 to 1.91×10^7 (mean ± SD 1.32 ± 0.31) for the controls (Lecky and Morgan-Hughes, 1981). The rate of toxin binding to the patient's AChR was also similar to that obtained in controls, the K_{+1} being $1.6 \times 10^4 \cdot M^{-1} \cdot s^{-1}$ (control range 0.9 to $2.7 \times 10^4 \cdot M^{-1} \cdot s^{-1}$). Affinities for d-tubocurarine and acetylcholine as indicated by the I_{50} values were also normal at 0.2 μmol/l and 0.1 μmol/l, respectively (Morgan-Hughes *et al.*, 1981).

Biochemical Studies

The total muscle carnitine concentration was normal (1.29 μmol/g wet weight). Values for 28 disease controls ranged from 1.08 to 3.87 μmol/g wet weight (mean ± SD 2.0 ± 0.7).

Respiratory activities of the patient's mitochondria oxidizing different substrates are given in Table 1. Similar data for control human muscle mitochondria quoted by

TABLE 1. RESPIRATORY ACTIVITIES OF ISOLATED SKELETAL MUSCLE MITOCHONDRIA

Substrate	*Patient type*	*State 3 rate*[a]	*RCR*[b]	*+TMPD*[c]	*Reference*
5 mM L-pyruvate (+malate)	Controls	92	3.0	—	Makinen and Lee (1968)
	Disease controls				
	V.H.*	75	4.6	96	This laboratory
	J.T.*	55	5.3	84	This laboratory
	Case M.A.	29	1.5	96	This paper
10 mM DL-glutamate (+malate)	Controls	68	1.9	—	Makinen and Lee (1968)
	Disease controls				
	V.H.*	72	2.9	ND	This laboratory
	Case M.A.	13	1.8	ND	This paper
50 μM DL-palmitoylcarnitine (+malate)	Case M.A.	19	—	86	This paper
10 mM DL-succinate (+rotenone)	Controls	55	1.7	—	Makinen and Lee (1968)
	Disease controls				
	V.H.*	99	—	ND	This laboratory
	J.T.*	51	3.7	ND	This laboratory
	Case M.A.	32	—	91	This paper
1 mM L-ascorbate (+rotenone and antimycin A)	Disease controls				
	V.H.*	—	—	251	This laboratory
	J.T.*	—	—	84	This laboratory
	Case M.A.	—	—	115	This paper

[a] State 3 rate in n atoms O/min/mg mitochondrial protein. [b] Respiration in the presence of ADP/respiration in the absence of ADP. [c] State 3 respiration rates in the presence of 50 μM tetramethylphenylenediamine. * V.H. and J.T. are disease controls studied in this laboratory. Substrate concentrations shown are those used in this laboratory. ND = not done.

Makinen and Lee (1968) and for muscle mitochondria isolated from two disease controls (V.H. and J.T.) which were studied in this laboratory are shown for comparison. In the latter two cases, no biochemical abnormality was detected. In the present case, mitochondrial O_2 uptake rates were depressed using both NAD-linked substrates and substrates linked by other flavoprotein systems, but some respiratory control was observed with pyruvate and with glutamate. The addition of the uncoupling agent carbonyl cyanide-p-trifluoromethoxy phenylhydrazone (FCCP) to these incubations failed to increase state 3 O_2 uptake rates indicating that the low respiratory activity observed with these substrates was not due to a deficiency of mitochondrial ATPase (Schotland *et al.*, 1976). With three of the substrates tested, namely pyruvate, succinate and palmitoylcarnitine, O_2 consumption was also monitored in the presence of tetramethyl-p-phenylenediamine (TMPD), an artificial electron acceptor which bypasses complex III by shuttling reducing equivalents directly from complex I or complex II to cytochrome c (Lee *et al.*, 1967). With this system, respiratory rates increased approximately threefold and approached those obtained with the artificial electron donor ascorbate + TMPD (Table 1).

These combined results suggested that the primary dehydrogenases of complex I and complex II and that portion of the respiratory chain between cytochrome c and oxygen were functionally intact and that the rate limiting step was localized to the CoQ-cytochrome bc_1 segment of the chain, that is, complex III. A low temperature spectrum of the mitochondrial cytochromes showed that absorption peaks normally present at 556 nm, the wavelength of reduced cytochrome c_1 and at 562 nm the wavelength of reduced cytochrome b were absent in this case (fig. 3A, B). A separate spectrum in which cytochrome b may be observed independently was obtained by incubating mitochondria in the presence of rotenone, succinate and

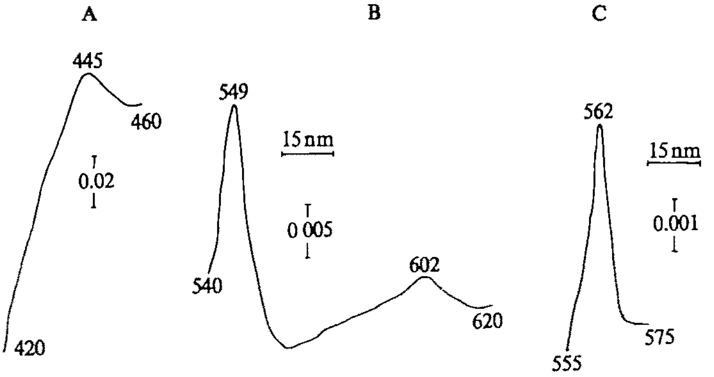

FIG. 3. Difference spectra (reducing minus oxidized) of the muscle mitochondria from patient M A. at the temperature of liquid nitrogen. A, gamma band; B, alpha band; C, difference spectra of the mitochondrial sample in which 5 μm rotenone, 10 mM succinate and 10 mg/ml antimycin A were present in the reduced sample. This leads to the reduction of only cytochrome b Alpha band: cytochrome a, 602 nm, cytochrome b, 562 nm; cytochrome c, 549 nm. Gamma band: cytochrome a_3, 445 nm.

antimycin A (fig. 3c). This indicated that cytochrome b was present but that its concentration was abnormally low relative to the concentration of cytochrome c and also when compared with cytochrome b levels in 2 disease controls and in 7 other patients studied in this laboratory in whom the defect was thought to be localized to the NADH-CoQ reductase complex (Table 2). Additional studies at more sensitive absorbance ranges, however, failed to reveal a shoulder or peak at or around 556 nm where cytochrome c_1 would be expected to absorb. The absolute level of cytochrome $a + a_3$ was also low in this mitochondrial preparation (Table 2) but it did not appear to limit the rate of ascorbate + TMPD mediated O_2 uptake significantly (Table 1).

The specific activities of citrate synthase, pyruvate dehydrogenase and NADH-ferricyanide reductase were such that they would not be expected to limit the state 3 O_2 uptake rates using the substrates tested (Table 3).

TABLE 2 CYTOCHROME CONTENT OF SKELETAL MUSCLE MITOCHONDRIA IN NMOL/MG MITOCHONDRIAL PROTEIN

Case	*b*(α-*564 nm*)	*c*(α-*550 nm*)	c_1(α-*556 nm*)	*a*(α-*602 nm*)	a_3(γ-*445 nm*)	*Reference*
A. From 2 disease controls studied in this laboratory.						
V H	0.48	0.74	0.48	0.50	0.26	This laboratory
J.T.	0.48	1.20	1.10	0.99	0.17	This laboratory
B. From 7 patients with a deficiency of the NADH-CoQ reductase complex in whom the mitochondrial cytochromes were considered to be normal						
M.F	0.79	1.06	0.67	0.96	0.60	Land *et al* (1981)
P D.	0.70	0.97	0.89	0.73	0.40	Morgan-Hughes *et al* (1982)
L.B.	0.29	0.62	0.43	0.18	0.12	Morgan-Hughes *et al.* (1984*a*)
C B	0.40	0.74	1.07	0.30	0.17	Morgan-Hughes *et al* (1984*b*)
G.N	0.75	1.02	0.80	0.35	0.28	Morgan-Hughes *et al* (1984*b*)
T R	0.40	0.57	0.47	0.43	0.19	Clark *et al* (1984)
C M	0.44	1.01	0.91	0.33	0.33	—
Mean ± SD	0.54 ± 0.2	0.85 ± 0.21	0.75 ± 0.24	0.47 ± 0.28	0.30 ± 0.16	
C. From patient						
M.A	0.17	0.84	—	0.11	0.08	This paper

TABLE 3 MUSCLE MITOCHONDRIAL ENZYME ACTIVITIES

	Activity (nmol/min/mg mitochondrial protein)		
		Disease controls	
Enzyme	*Patient M.A.*	*V.H.*	*J.T.*
Citrate Synthase	3092 (latency 20)	895	1368 (latency 13)
Pyruvate dehydrogenase	62	84	106
NADH-ferricyanide reductase	548	ND	ND

Enzyme activities were measured at 25° C and are expressed as the mean of two estimations at different protein concentrations. The latency of citrate synthase represents the activity in the presence of 0.1 per cent Triton divided by the activity in its absence ND = not done.

DISCUSSION

These studies have shown that mitochondria isolated from this patient's muscle exhibited very low O_2 consumption with substrates which would normally be utilized *in vivo*. Measurement of enzyme activities and latency (Table 3) suggested that this was not due to a primary deficiency in the activity of a substrate dehydrogenase or the citric acid cycle, nor to an artefact of mitochondrial isolation. Data obtained with the TMPD shunt method of Lee *et al.* (1967) suggested that the rate limiting step was localized to the respiratory chain and involved the ubiquinone-cytochrome bc_1 complex. This was supported by the results of low temperature spectroscopy which showed an abnormally low absolute concentration of reducible cytochrome b and what appeared to be a total deficiency of cytochrome c_1. However, it is difficult to reconcile the O_2 uptake data (Table 1) with absence of this cytochrome unless electrons were being passed directly between cytochrome b and c an event for which there is no precedent. It must be assumed, therefore, that some albeit limited amount of cytochrome c_1 was present. The failure to detect it may have been due to altered spectral characteristics or to a low absolute concentration such that its absorbance band was hidden in the cytochrome c peak. The low level of cytochrome b was also undetectable in the overall spectrum but was readily observable when an independent spectral analysis was performed. Cytochrome c_1, however, cannot be analysed independently by this method.

The major clinical feature in this patient, in common with other reported cases, was exercise intolerance but mild nonfatiguable ptosis was also noted. The morphological changes in the two muscles examined were essentially similar and indicated that the biochemical error was being expressed in both. The normal EMG and radiochemical studies indicated that the defect was not expressed at the level of the neuromuscular junction. Virtually all the ragged red fibres in both muscles showed no detectable cytochrome c oxidase activity on histochemical analysis, a finding which may have explained the low absolute levels of cytochrome $a+a_3$ as determined by low temperature spectroscopy. The low absolute concentration of cytochrome $a+a_3$ did not significantly limit the rate of TMPD-mediated respiration (Table 1). In 10 other patients with mitochondrial myopathies studied in this laboratory, no clear-cut correlation between the level of cytochrome $a+a_3$ and ascorbate+TMPD respiration rates has been observed (D. J. Hayes, unpublished data). The relevance of this histochemical observation to mitochondrial function remains to be determined.

The components of complex III, namely cytochromes b and c_1, an iron sulphur protein, two hydrophobic core proteins, the antimycin A binding site protein and 6 other polypeptides (Rieske, 1976) are coded for by both nuclear and mitochondrial DNA (Schatz, 1979; Ernster and Schatz, 1981). In yeast, human and bovine species, the cytochrome b gene is located within the mt DNA (Schatz, 1979; Ernster and Schatz, 1981; Anderson *et al.*, 1981, 1982), whilst it is known that in yeast, cytochrome c_1 and subunit 5 are coded for by nuclear DNA (Schatz, 1979; Ernster and Schatz, 1981). The location of the other gene components of complex III remains to be established.

Studies on yeast cells have revealed numerous cytochrome b deficient strains some of which were due to mutations in the mitochondrial genome (Solioz and Schatz, 1979). More recently Diekmann *et al.* (1982) have obtained cytochrome b deficient strains with nuclear mutations. They suggested that defective mRNA processing, normally mediated by nuclear coded enzymes, could be responsible for the lack of cytochrome b. A similar study on Chinese hamster lung cell mutants has revealed that some cell strains which were unable to grow in a galactose medium also exhibited defective mitochondrial oxidation (Malczewski and Whitfield, 1982). These mitochondria had low NADH-CoQ reductase and ATPase activities and diminished levels of cytochrome $a + a_3$. These multiple defects were clearly the result of a single mutation as each of the affected activities was simultaneously corrected in a spontaneous revertant. These workers suggested that the decreased activities of several respiratory complexes might be due to a mutant protein that was needed for the insertion or assembly of respiratory chain subunits within the mitochondrial inner membrane. Alternatively these mutant cells may have lacked a protease required for the processing of precursor polypeptides or a nuclease involved in the formation of a mature RNA transcript. Cytochrome c_1 which is synthesized in the cytoplasm is initially formed as a precursor (Schatz, 1979) which is some 60,000 Daltons larger than the mature cytochrome c_1. The import of this apocytochrome requires the mitochondrial membrane to be energized (Schatz, 1979; Ohashi *et al.*, 1982). At least two proteolytic processing steps are involved, the second of which is thought to be in conjunction with haem binding (Ohashi *et al.*, 1982). These studies support the view that mitochondrial proteins synthesized in the cytosol are processed to a final form which is then suitable for correct assembly within the mitochondrial inner membrane.

The most probable cause of this patient's defect would seem to be a single gene mutation possibly involving a protein required for the correct assembly of complex III. A somewhat similar patient has recently been reported by Darley-Usmar *et al.* (1983), although in their case cytochrome c_1 levels were normal.

ACKNOWLEDGEMENTS

This work was generously supported by the Muscular Dystrophy Group of Great Britain and the Brain Research Trust and some of the equipment was provided by the Mason Medical Foundation. We thank Mr Richard Hayward and Mr Peter Crawford for carrying out the muscle biopsies and Mrs Marjorie Gilbert, Mr Brian Young and Miss S. D. Nursey for their technical assistance. One of us, D.J.H., holds a Brain Research Trust Fellowship which is gratefully acknowledged. We also thank Dr Andrew Bowden for referring the patient.

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(*Received February 24, 1984. Revised June 7, 1984*)

Brain (1984), **107**, 1179-1188

EVIDENCE FOR DIFFERENT MECHANISMS OF PRIMARY AND SECONDARY HYPERALGESIA FOLLOWING HEAT INJURY TO THE GLABROUS SKIN

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SUMMARY

Characteristics of primary (within the area of injury) and secondary (outside the area of injury) hyperalgesia were determined after a heat injury applied to the glabrous skin of the hand in 8 human volunteers. The heat injury consisted of two burns (53° C, 30 s) applied over an area 7.5 mm in diameter separated (centre to centre) by a 2 cm interval. Following the injury, a zone of hyperalgesia to mechanical stimuli measuring 20.1 ± 3.6 cm^2 (mean ± SEM) developed in an area surrounding and including the burns. Within this zone, the pain threshold for mechanical stimuli decreased significantly by a similar amount for all areas tested (12.0 ± 1.1 bars to 5.2 ± 0.5 bars). Hyperalgesia to heat occurred only within the area of the burns. The heat pain threshold decreased and total ratings of heat pain increased significantly. In contrast, there was decreased pain to heat stimuli between the two burn sites, and no change in painfulness of the heat stimuli at other areas within the zone of hyperalgesia to mechanical stimuli. Particularly notable was the coexistence of *hypalgesia* to heat stimuli and *hyperalgesia* to mechanical stimuli in the uninjured region between the two burn sites. These results indicate that the characteristics of primary and secondary hyperalgesia differ and also suggest that the mechanism for hyperalgesia to mechanical and thermal stimuli differ.

INTRODUCTION

Hyperalgesia is an altered state of cutaneous sensibility characterized by a decrease in pain threshold, an increase in pain to suprathreshold stimuli and often spontaneous pain. Distinctions have been made between two forms of hyperalgesia—primary hyperalgesia, occurring within the area of injury, and secondary hyperalgesia, occurring outside the area of injury.

While there is general agreement regarding the nature of primary hyperalgesia, disagreement exists concerning the characteristics of secondary hyperalgesia (Lewis, 1933, 1935, 1942; Hardy *et al.*, 1950). Hardy and his collaborators and Lewis agreed that hyperalgesia to both mechanical (mechanical hyperalgesia) and

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heat stimuli (thermal hyperalgesia) was present at the site of injury and that hyperalgesia to mechanical stimuli was present in the region surrounding the injury. They disagreed, however, regarding the painfulness of heat stimuli in the area surrounding the injury. Lewis reported that a 'lowering of pain threshold to heat is suspected to occur from time to time; but the effect, when present, is slight' (Lewis, 1942, p. 70). Hardy *et al.* (1950) reported that the heat threshold for pain was unchanged, but suprathreshold heat stimuli produced augmented pain. These differences in findings prompted us to reexamine the psychophysical changes that occur in the region of primary and secondary hyperalgesia following a thermal injury. Preliminary results have been reported (Raja *et al.*, 1983).

METHODS

Subjects and Stimulation Techniques

Responses to mechanical and thermal stimuli before and after heat injury of the skin were tested in 8 subjects (7 male, 1 female), who ranged in age from 23 to 37 years. Two subjects were tested twice and thus there were 10 experiments. Informed consent was obtained from all subjects. Heat stimuli and burns were applied to the skin with use of the previously described CO_2 laser thermal stimulator (Meyer *et al.*, 1976; LaMotte and Campbell, 1978). Stepped increases in skin temperature were applied for specified periods to a 7.5 mm diameter spot. Times to reach the desired temperature ranged from 80 to 140 ms for each stimulus. A radiometer remotely detected skin temperature and provided feedback control of the laser power, thus obviating the need for mechanical contact with the skin. This proved particularly advantageous in this study since sensitivity to mechanical and heat stimuli could be assessed independently.

Sensitivity to heat stimuli was tested by use of a thermal test sequence. The stimuli varied in 1° C increments from 41 to 49° C, and were 3 s in duration. The stimuli were presented every 30 s in random order except for two constraints: (1) the 45 ° C stimulus was given twice, once as the first stimulus, and again as part of the random sequence; and (2) each of the stimuli other than 45° C was given only once per sequence. A 38° C base temperature was applied for 1 min before the first stimulus and between stimuli. The painfulness of the stimuli was rated by subjects using the technique of magnitude estimation (Stevens and Galanter, 1957). Subjects assigned an arbitrary number, the modulus, to the magnitude of the pain evoked by the first 45° C stimulus of the first test sequence in a given test session. This stimulus was considered painful by all subjects. Subjects then judged the painfulness of subsequent stimuli for the remainder of the test session relative to the modulus. For example, if the modulus was 10 and a subsequent stimulus was judged to be twice as painful, then the subjects were instructed to rate that stimulus 20. Nonpainful stimuli were assigned a rating of 0. Test runs were given to assure that subjects understood the procedure. The technique of magnitude estimation and the thermal test sequence were used by us in previous studies (Meyer and Campbell, 1981; Campbell and Meyer, 1983).

Thresholds for mechanically induced pain were determined by free-hand application of calibrated nylon monofilaments. The nylon probes were applied by using the technique of ascending series to the centre of each of the test areas (spots A, B and C in fig. 1). The pain threshold was considered to be that pressure which the subject felt confidently to be painful. The border between the region of mechanical hyperalgesia and normal skin was determined by dragging a nylon monofilament probe 0.83 mm in diameter across the skin. Subjects described a well-defined border between normal and hyperalgesic skin. This border was marked on the skin with a pen. This stimulus did not evoke pain before injury, but did evoke pain in the affected area after injury. The area of flare and hyperalgesia was measured by tracing with a planimeter the outline of the relevant zone on a photocopy of the hand.

Protocol

Sensitivity to the mechanical and heat stimuli was tested before and after a heat injury which consisted of two burns. The configuration of test areas (spots A, B and C) and location of the two burns (spots A and D) are shown in fig. 1. The burn consisted of a 53° C, 30 s stimulus. This burn stimulus was used by us previously (Meyer and Campbell, 1981), and results in a blister after about 2 h about 50 per cent of the time. Spots A, B and D were positioned at 10 mm intervals on the thenar eminence along a straight line. Since the diameter of the laser stimulus was 7.5 mm, heat stimuli centred on one test spot did not heat other test spots. Specifically, burns at spots A and D therefore did not heat spot B. The location of spot C was 15 mm from the A-B-D line and was chosen to be near the expected edge of the flare but within the expected area of secondary hyperalgesia.

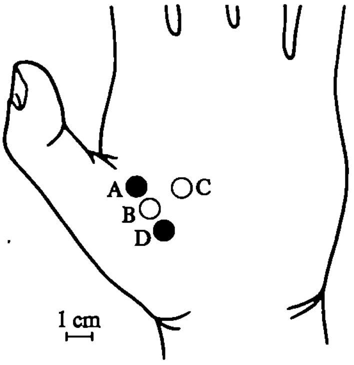

FIG. 1. The relative location of the stimulus sites on the glabrous skin of the hand are shown. Mechanical thresholds for pain and ratings of pain to heat stimuli were recorded at sites A, B and C before and after burns at sites A and D. The burns consisted of a 53° C, 30 s stimulus at both sites.

The mechanical and thermal tests at the different sites were undertaken in the following sequence. (1) Pain thresholds to mechanical stimuli were determined at sites A, B and C using nylon monofilament probes. (2) Ratings of painfulness to the heat stimuli at sites A, B and C were recorded by use of different thermal test sequences for each site. For a given site, the sequence used in a given experiment was the same. The choice of sequence was randomized for each site and between subjects. (3) The burns were applied to sites A and D. (4) Five minutes after the double burn, pain thresholds to mechanical stimuli were determined at sites A, B and C. The area of mechanical hyperalgesia and flare was mapped. (5) Ten minutes after the burn, ratings to heat stimuli were again recorded at sites B, C and A, respectively. (6) The area of hyperalgesia to mechanical stimuli and the mechanical pain thresholds were redetermined after the thermal tests.

In 4 subjects, the detection threshold to mechanical stimuli was also tested with the nylon monofilament probes before and after the double burns. Student's t test was used for statistical analysis unless otherwise noted.

RESULTS

Effects of Thermal Injury on Painfulness of Mechanical Stimuli

The mean thresholds for pain evoked by mechanical stimulation at sites A, B and C before and after the double burn injury are shown in fig. 2. Before injury, the pain threshold was 12.0 ± 1.1 bars (mean ± SE, 1 bar = 10^6 dynes/cm^2) and was similar at the three sites tested. After injury, the pain threshold decreased significantly

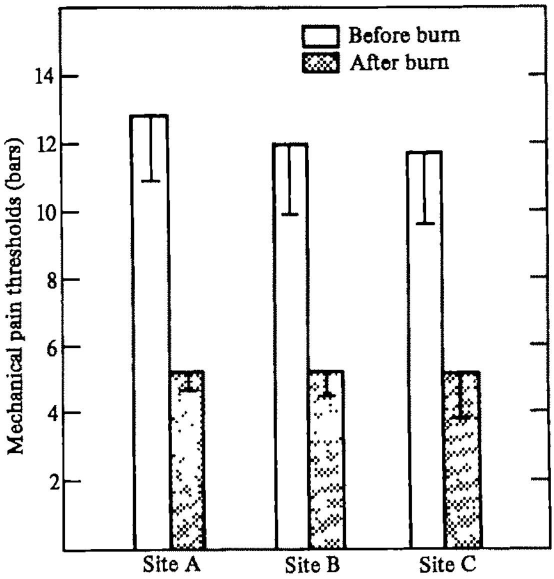

FIG. 2 Mean mechanical thresholds for pain before and after the burns (N = 7). The mechanical threshold for pain was significantly decreased following the burn. The mechanical hyperalgesia was of similar magnitude at each of the three test spots (A, B, C). Error bars correspond to SEM.

(5.2 ± 0.5 bars, $P < 0.001$). As shown in the figure, the pain thresholds were similar at the three sites. The threshold for detection of mechanical stimuli before (0.83 ± 0.12 bars) and after (0.82 ± 0.16 bars) the thermal injury were not significantly different. In all subjects, the detection thresholds were lower than the pain thresholds both before and after the thermal injury.

The hyperalgesic area (20.1 ± 3.6 cm^2) mapped about 30 min after the injury was significantly larger than the maximal area of the flare (8.3 ± 0.8 cm^2; $P < 0.01$). Results for a typical subject are shown in fig. 3. The area of hyperalgesia mapped 30 min after the burns was larger than that observed 5 min after the injury. The flare reached its maximal area in less than 10 min and typically disappeared within an hour after the injury, whereas the mechanical hyperalgesia persisted for several hours.

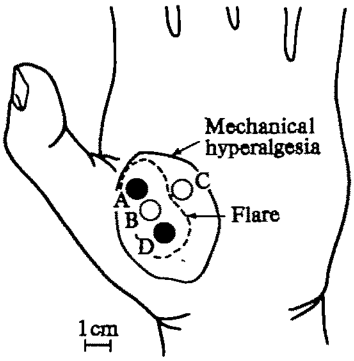

FIG. 3. Relationship between area of flare and area of mechanical hyperalgesia following the burns in one subject. In all subjects, the area of mechanical hyperalgesia was larger than the area of flare. Mechanical hyperalgesia was present even after the flare disappeared.

Effects of Thermal Injury on Painfulness of Heat Stimuli

The judgements of magnitude of pain to the heat stimuli at sites A, B and C before and after the burns are shown in fig. 4. The rating to a given stimulus was normalized for each subject by dividing by the modulus, that is, the rating given by the subject to

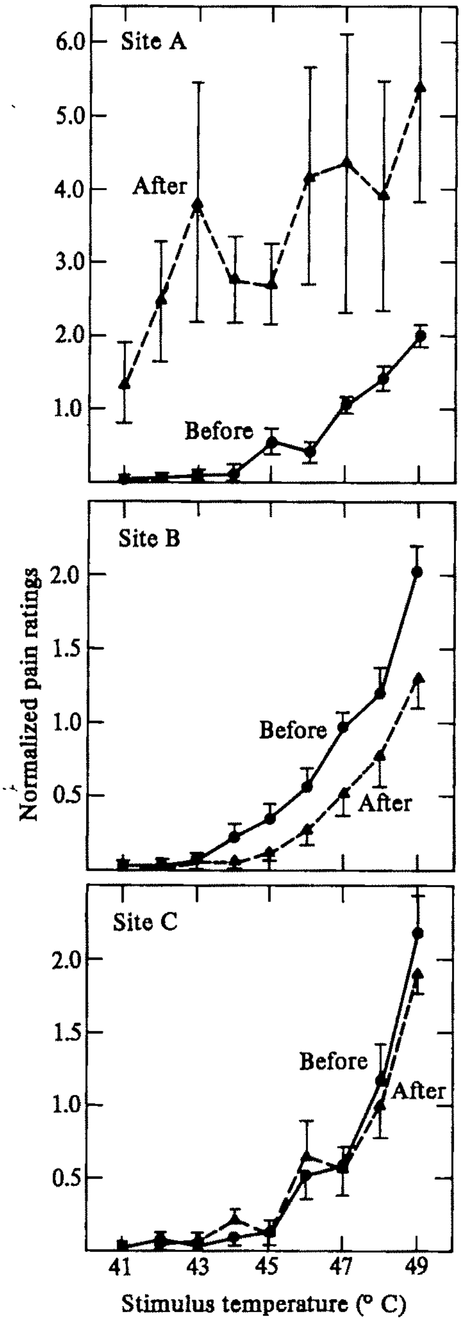

FIG. 4. Mean normalized ratings of painfulness of stimuli before and after the burns. Ratings were normalized for each subject by dividing the ratings to a given stimulus by the rating to the first 45° C stimulus presented to the subject. At site A, all the characteristics of thermal hyperalgesia (i.e. decrease in pain threshold, increase of pain to suprathreshold stimuli and spontaneous pain) were observed after the burns (n = 8). At site B, pain ratings decreased after the burns. Thus, thermal hypalgesia was observed (n = 9). At site C, pain ratings before and after the burns were not significantly different (n = 8).

the first 45 ° C stimulus of the first run. Before the injury, the normalized pain ratings to the different temperature stimuli were similar for all three sites (note that the scale for site A in fig. 4 is different from that for sites B and C). Site A was markedly hyperalgesic to heat stimuli following injury with a substantial decrease in pain threshold, and a marked increase in pain to suprathreshold stimuli. The pain threshold prior to injury was 43.4 ± 0.5 ° C. After the injury, the pain threshold decreased to below 38° C since all subjects rated the onset of base temperature (38° C) as painful (Wilcoxon signed rank test for paired design, $P < 0.01$). In contrast, site B, was *hypalgesic* after the double burns. The pain ratings to suprathreshold stimuli at site B were lower after the injury than before. The pain ratings at site C were similar before and after the thermal injury.

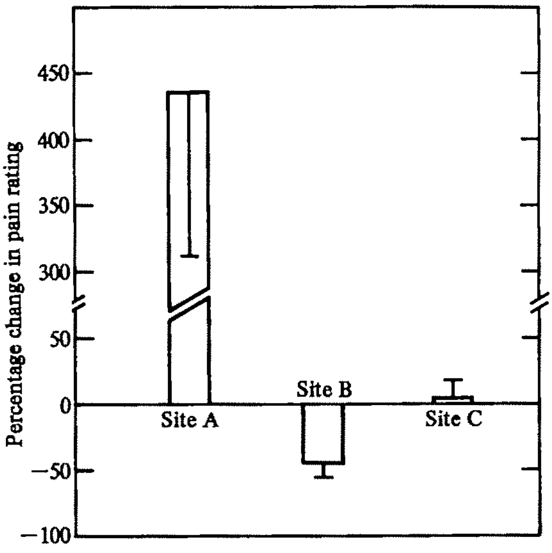

FIG. 5. Mean percentage change in ratings of painfulness of heat stimuli after the burns. At site A, the pain ratings increased more than fourfold after the burns. At site B, the pain ratings decreased by 50 per cent following the burns. At site C, no significant change in pain ratings was observed. Thus, thermal hyperalgesia was observed only at the site of the burn, whereas thermal hypalgesia was observed in the uninjured area between two burns.

To illustrate further the changes in ratings of pain at sites A, B and C, the sum of the responses to the sequence of heat stimuli was computed in each subject. Fig. 5 shows the percentage change of the ratings after the double burns for each of the 3 sites tested. At site A, there was more than a fourfold increase in magnitude of pain (440 ± 120%, $P < 0.01$), while at site B, there was nearly a 50 per cent decrease in ratings of pain (−46 ± 10%, $P < 0.005$). At site C, little or no change in ratings was evident (3 ± 13%). Thus hyperalgesia to thermal stimuli occurs only at the site of the burn, whereas hypalgesia occurred between the two burns.

DISCUSSION

The results of this study indicate that the characteristics of the hyperalgesia following a cutaneous burn are different within as opposed to outside the boundaries of the injury. Within the zone of injury (region of primary hyperalgesia), hyperalgesia is present to both heat and mechanical stimuli. In the region surrounding injury (zone of secondary hyperalgesia), hyperalgesia is present only to mechanical stimuli.

It might be argued that the failure to find hyperalgesia to heat stimuli outside the area of injury means that the psychophysical paradigm used in this study lacked sufficient sensitivity. However, in the uninjured area between two burns, a reduced sensitivity to heat (i.e., hypalgesia) occurred simultaneously with hyperalgesia to mechanical stimuli. This dissociated sensory change supports the conclusion that the mechanisms of primary and secondary hyperalgesia are different, and also suggests that the mechanism for hyperalgesia to mechanical and thermal stimuli differ.

The findings presented here regarding the nature of secondary hyperalgesia are at odds with those of Hardy and his collaborators, who reported enhanced pain to threshold and suprathreshold heat stimuli, but no change in heat threshold to pain (Hardy *et al.*, 1950). A methodological artefact could account for this discrepancy. Hardy used a controlled energy radiant heat stimulus. If the base temperature increased after the injury, as might be expected in the zone of flare, the energy necessary to reach a given temperature would be less, leading to the spurious conclusion that hyperalgesia to heat stimuli was present. Use of the laser thermal stimulator in our study obviates this problem, since skin temperature is monitored and controlled. R. H. LaMotte and colleagues (personal communication), using a contact thermode, also did not find evidence of thermal hyperalgesia in the zone of secondary hyperalgesia following a heat injury.

The hyperalgesia to heat following injury is thought to be mediated by the sensitization of nociceptive afferents (Bessou and Perl, 1969; Beitel and Dubner, 1976; Kumazawa and Perl, 1977; LaMotte *et al.*, 1983). C-fibre nociceptive afferents (CMHs) in the hairy skin (LaMotte *et al.*, 1982; Campbell and Meyer, 1983) and A-fibre nociceptive afferents (AMHs) in the glabrous and hairy skin (Fitzgerald and Lynn, 1977; Campbell *et al.*, 1979) have lower heat thresholds and an increased response to suprathreshold stimuli following a heat injury which correlates with hyperalgesia to heat stimuli in human subjects (Meyer and Campbell, 1981; LaMotte *et al.*, 1982). Heat injuries adjacent to or partially overlapping the receptive fields of AMHs and CMHs do not alter the heat response in the uninjured part of the receptor (Thalhammer and LaMotte, 1982), which provides neurophysiological evidence consistent with the psychophysical finding that hyperalgesia to heat does not occur outside the site of injury.

The basis for hyperalgesia to mechanical stimuli in the primary and secondary hyperalgesic region has not been established. Heat injuries to the receptive field of CMHs (R. H. LaMotte, personal communication) and AMHs (Campbell *et al.*, 1979), sometimes result in a lowering of the mechanical threshold which might account for the primary hyperalgesia to mechanical stimuli. Heat injuries adjacent to the receptive field of AMHs and CMHs result in a slight expansion of the mechanical receptive field into the injury area without a change in mechanical threshold (Thalhammer and LaMotte, 1982). Although this might account for the hyperalgesia immediately adjacent to the injury due to recruitment, it cannot account for the pronounced hyperalgesia several centimetres away from the injury site. It may be that cutaneous injury enhances the sensitivity of central neurons related to pain perception such that they respond to input from low threshold mechanoreceptors (Lynn, 1977; Woolf, 1983). Conversely, the central input of nociceptors that innervate the region adjoining injury may somehow be facilitated by the sensitized nociceptors that innervate the region of primary hyperalgesia (Campbell and Meyer, 1985).

Secondary hyperalgesia and the flare response or reddening that surrounds an area of injury have been linked since Lewis's original description of these responses (Lewis, 1935, 1942). It has been suggested that the substances that induce the flare also sensitize nociceptors thus leading to hyperalgesia. However, there is evidence against this hypothesis. Most important, certain agents such as histamine dihydrochloride, when injected intradermally, elicit flare with little or no pain or hyperalgesia (Becerra-Cabal *et al.*, 1983). Also, as noted in this study, the area of the flare is significantly less than that of hyperalgesia. Additionally, the flare may last only a few minutes, whereas secondary hyperalgesia may last for several hours.

The mechanism for reduced sensitivity to heat stimuli (hypalgesia) between the two areas of injury could relate to central or peripheral factors. Fatigue is a prominent property of CMHs (LaMotte and Campbell, 1978). The injury stimulus excites parts of the receptive field of some nociceptors whose remaining receptive field lies in the zone between the two areas of injury. Stimulation of one part of the receptive field could suppress the response to stimulation of another part. Another possibility is that central neurons which signal pain to heat stimuli in the region between the two injury foci are suppressed by tonic or prior discharge of sensitized neurons within the zones of injury.

This study was concerned with the consequences of heat injury. A note of caution is in order before these findings can be extrapolated to other assaults to the skin. Bilisoly *et al.* (1954) reported that in the zone of flare resulting from an intradermal injection of noxious agents, both mechanical and thermal pain thresholds were lowered.

In future studies of hyperalgesia it will be important to distinguish those changes that occur in the primary as opposed to the secondary hyperalgesic site. Hyperalgesia to mechanical stimuli may occur in the absence of hyperalgesia to heat stimuli, and thus mechanisms for each should be considered separately. Such distinctions may also prove useful in classifying and treating clinical syndromes associated with hyperalgesia such as painful neuropathies, nerve entrapments, causalgia and reflex sympathetic dystrophy.

ACKNOWLEDGEMENTS

We gratefully acknowledge the technical assistance of Miss Trudy Lund, Mr Adil Khan and Mr Ronald Burke and the assistance of Mrs Faith Ford-Hardy in the preparation of the MS. This research was supported in part by NIH grant NS-14447, a Teacher Investigator Award, NS00519 to J.N.C. and a New Investigator Research Award, GM33451 to S.N.R.

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NOTICES OF RECENT PUBLICATIONS

The Human Mystery. By Sir John Eccles. 1984. Pp. 255. Henley-on-Thames: Routledge and Kegan Paul. Price £5.95 (soft cover).

Sir John Eccles' Gifford Lectures originally published in the United States in 1978 have now been republished in England, which provides an opportunity to discuss his striking thesis. When anyone who is seriously interested in the brain reads the views of a dualist he surely asks the question 'How does he think that it works?' If there is some nonmaterial agency operating upon the brain it is the neuroscientist's job to find out how and where its effects are exercized. With his great knowledge of cerebral physiology Eccles must often ask this question, and he should be in an ideal position to direct his attention to it. A detailed answer to it would indeed be interesting to all physiologists. It would help greatly to solve one of the most difficult of our problems by showing which neurons are active when we perform some simple task, say identifying and naming a face. Eccles at first seems to attack the problem directly and to provide his own answer. After a full and careful description of modules in the cortex he writes 'So the re-constitution of the retinal image as a perceived picture requires some synthetic operation that reads out from the modules and rebuilds the picture. This picture is perceived in the mind. It is a mistake to think that it can therefore be discovered in the brain, where instead there is only the coded information in countless neuronal discharges.'

So, 'the self-conscious mind scans and reads out from the appropriate feature recognition modules of the visual areas'. But this formulation does not provide the details which even the dualist should ask for. Descartes put the action of the soul in the pineal body. Eccles has only the 'appropriate feature recognition modules'. If he could show us which they are it would then be possible to make actual tests of what happens when the mind has its influence on what he calls the 'gentle level' of cortical pyramidal cells, perhaps by inhibition in laminae I and II. 'A very gentle deviation up or down is all that is required.'

One might (unwillingly) concede that there could possibly be such influences at some microscopic subatomic level. If they are to control behaviour they must produce changes at the macroscopic level, say of membrane potentials. Surely it is the business of a serious dualist physiologist to suggest ways of finding and testing the appropriate modules. Indeed perhaps it should not be too difficult since it is supposed that the action cannot be on single cells but upon 'ensembles of neurons (many hundreds) acting in some collusive patterned array'. But there is no evidence of such a search in the book. Nor is there even a suggestion of means by which such evidence might be found, *nor that Eccles himself has looked for it.*

The whole fabric is therefore purely a guess, no better than the alternative—most of us guess that an answer will be found that does not invoke a 'loophole in the apparent closedness of the world of matter and energy'. We hope to find some other solution than scanning by the self-conscious mind. Time will (eventually) show who is right.

Eccles is indeed well aware of the need to find some evidence for his theory and he suggests that the split brain phenomena provide this. Sperry might agree with him, but Sperry seems to invoke *two* distinct minds, that in the right hemisphere being obscured by its lack of expressive language. Eccles evades this unwelcome plethora of minds by saying that 'we do not know if there is some inexpressible consciousness in the isolated right hemisphere, just as we do not know of any consciousness animals might have'. This solution is a trick, getting rid of a debt by borrowing to double it.

He also uses evidence from the readiness potentials, which are recorded when a subject initiates movement at will. This is certainly a valuable way of showing that 'there is a developing specifity of the patterned impulse discharges in the neurons'. It is not clear how it helps the dualist thesis. Eccles says it shows 'that the action of the self-conscious mind on the brain is not of demanding strength. We may regard it as being more tentative and subtle, and as requiring time to build up patterns of activity . . .'. The delay does indeed show that complicated processes are at work, but this is not evidence that they are the product of an intervening mind.

Libet has used the readiness potential to even greater effect by finding a way of getting subjects to record the moment at which they decide to make an action. His early conclusions are quoted as supporting Eccles' theory, but the latest results (*Brain*, **106**, 623–642, 1983) showed that the brain is at work 350 ms *before* any conscious decision is taken. This most interesting finding is, if anything, contrary to the dualist thesis. As Libet and his colleagues cautiously put it, this 'would appear to introduce certain constraints on the potential for exerting conscious initiation and control over his voluntary acts'. Indeed it does. Some might say, less cautiously, that it shows that the brain initiates or 'causes' the conscious state of willing. This is one of the most important findings in the whole history of the mind-body problem.

It would be interesting to know how many neurophysiologists can be found who would support the dualist theory. Probably not many, but we should be grateful to Jack Eccles for putting out his theory so honestly and bravely. It is very good for us to be shown just how difficult the problem is and how far we are from providing an alternative solution.

Incidentally, one can be grateful also for the rest of the lectures, in which he gives good summaries of the origins of everything from the Universe to Man. He remains agnostic about natural selection. After putting down most of the facts accurately he gives full credit to Darwinian theory 'as one of the grandest conceptual achievements of man'. But then at the end of the book he has 'grave misgivings'. Unfortunately this gives welcome support to the Creationists, who wish to discredit the 'grandest conceptual achievement'.

The lectures provide an easily readable summary of many aspects of science and especially of brain physiology. For my taste, though, they would be much better if Eccles had never become involved in all that Three Worlds stuff with Popper. I suppose one might argue that it is only a harmless *façon de parler*; but surely one world is enough to puzzle over. The problems of the nature of mentality and consciousness are at the root of all philosophy and science. Eccles faces them best as a physiologist, when he is not trying to be a philosopher focusing on three worlds at once.

J. Z. YOUNG

Selected Papers of Morris B. Bender. Memorial Volume. Edited by Robert P. Friedland. 1983. Pp. 463. New York: Raven Press. Price $60.00.

This memorial volume of selected papers by Dr Morris Bender is a fitting tribute to a great neurologist. The papers were selected and their publication planned, with his approval, as a tribute to him before his death in 1983 at the age of 77, so that they include what he, as well as his colleagues, thought were the most important of his contributions. They range widely from his work in experimental neurophysiology with Fulton at Yale to the medical management of patients with subdural haematoma. Experimental and clinical studies concerned with the problems of ocular motility and visual perception form a large part of this volume. The 14 papers on oculomotor function are of great interest, showing as Dr Bernard Cohen points out, 'how our understanding of the basic groundwork of the oculomotor system has come about'. The second large group of papers in this collection is chosen from his extensive work on the problems of visual and sensory perception and show too how ideas on this difficult subject developed during a period of over forty years.

The paper on the medical management of subdural haematoma is in some ways the most remarkable of all. Macdonald Critchley, who knew him well, in an introduction to this volume wrote that Bender's aim 'has always been the welfare of his patients . . . always investing them with his aura of warmth and understanding'. It can only have been someone able to achieve an exceptional relationship of trust with his patients who could have carried out this work at all, particularly in view of the controversy naturally provoked by his views.

It is sad that the volume planned as a tribute to the living should have been published after his death, but it is a happy thought that he did his last ward round the day before he died.

C. J. Earl

Contemporary Neurology. Edited by M. J. G. Harrison. 1984. Pp. 641. London: Butterworths. Price £25.00 (paperback).

Dr M. J. G. Harrison has been involved over the past ten years in commissioning review articles on neurological topics for the *British Journal of Hospital Medicine*. This book consists of 64 chapters, mainly based on such articles but revised to bring them up to date, together with some specially written for the book. They cover a wide range of subjects, the emphasis being on practical management. The chapters are thus on the diagnosis and treatment of the commoner neurological conditions, and include a number devoted to the performance of practical procedures. Pathophysiology and disease mechanisms figure only incidentally. The individual contributions are didactic in style and would be particularly suitable for trainees in medicine or neurology, working, for example, for the MRCP (UK) or the American 'Board' examinations. As might be expected with such a large number of contributors, the presentation and content are somewhat variable in quality, but overall the book admirably fulfils its intention of providing helpful accounts of contemporary neurological practice.

P. K. Thomas

Neurologic Emergencies. Edited by Michael P. Earnest. 1983. Pp. 534. Edinburgh: Churchill Livingstone. Price £42.00.

Dilemmas in the Management of the Neurological Patient. Edited by Charles Warlow and John Garfield. 1983. Pp. 285. Edinburgh: Churchill Livingstone. Price £23.00.

The first of these contrasting books is intended for junior staff in general medicine. It is clearly written, well illustrated and appropriately didactic and authoritarian; established clinical neurologists who need this book should consider premature retirement.

The content and philosophy of the second book will surely interest all clinicians irrespective of experience and sophistication. The editors posed twenty-five controversial dilemmas in neurological management and the challenge was accepted by selected authorities—with varying degrees of success—to sift available facts from opinions. Most of the problems are common—for example, do anticoagulants prevent embolism from the heart to the brain and does speech therapy influence the course of recovery from aphasia after a stroke? All the chapters are impressively lucid, succinct and well edited.

In their thoughtful and provocative introduction, the editors identify certain general characteristics of such clinical dilemmas when doubt, scepticism and uncertainty conflict with conventional recommendations. They also consider some of the unpalatable reasons why so many of these problems remain unresolved. Amongst these they emphasize our inability to organize and contribute to randomized controlled trials and the paucity of adequate clinical records and post-mortem information. They conclude with the chilling condemnation that 'the causes of failure are not financial but a lack of motivation and inclination to muddle on'. Few could deny out guilt, although there are less obvious but important mitigating factors to be considered in individual trials. Little persuasion is needed as to the necessity and importance of carefully designed trials to determine the efficacy of a new drug and it might be construed as unethical to recommend a new medication that had not been assessed in a placebo controlled trial. Nevertheless, it cannot be denied that certain trials may place considerable strains on doctor-patient relationships. Consider a randomized controlled study of the effects of neurosurgical treatment on slowly evolving conditions such as syringomyelia. Referring physicians would not be indifferent to the contrasting impacts of different regimens on their patients. As recently enunciated by Angell (Angell, M. (1984) Patients preferences in randomised clinical trials. *New England Journal of Medicine*, **310**, 1385–1387), it is not enough for the physician to have no reason to prefer one treatment over the other; in addition there must be no reason for the patient to prefer one treatment. Angell further considers the ethical as well as the scientific objections to trials involving patient preferences, the validity of trials with slow rates of patient entry during which prevailing conditions may change, the limitations of prerandomization, and the validity of comparable methods designed to encourage patient referrals. She also discusses the adequacy of nonrandomized historical or concurrent controls and the insoluble predicament of certain problems when it may not be ethically acceptable to conduct a valid randomized clinical trial. There are considerations other than apathy why physicians may be reluctant to collaborate in controlled trials.

The final chapter of this stimulating book analyses some of the reasons why evaluation of the relative merits of different treatments for the same condition may give apparently conflicting results. The logic of method and statistical analysis is briefly and coherently stated and it is laudable that those who are endowed with such mathematical abilities can also remain sensitive to philosophical reservations concerning absolute solutions. The epilogue quotes Karl Popper so aptly that it is worthy of repetition 'for the simple truth is often hard to come by, and that once found it may easily be lost again. Erroneous beliefs may have an astonishing power to survive, for thousands of years, in defiance of experience, with or without the aid of conspiracy. The history of science and especially medicine could furnish us with a number of examples.'

GERALD STERN

Topical Diagnosis in Neurology. By Peter Duus. Translated by Richard Lindenberg. 1983. Pp. 471. Stuttgart: Thieme. Price DM 38.00.

Neurology. A Textbook for Physicians and Students. By Mark Mumenthaler. 1983. Pp. 538. Stuttgart: Thieme. Price DM 30.00.

Until the midthirties it was customary for most English-speaking students of neurology and psychiatry to travel to continental Europe, especially Germany and France, to study the clinical and scientific methods employed in clinics and laboratories in these countries before settling in practice in Britain and the USA. The separation between psychiatry and neurology, now so entrenched a feature of Western medicine, had not then become so rigid. There was a well-established tradition, particularly in German neurology, for study of the brain and its behaviour. While these traditions have persisted in British and American neurological practice, their influence has diminished since the Second World War. Indeed, in recent years, so strong has been the emphasis on the one hand on biochemical and other techniques dependent on biopsy in the investigation of neurological problems and, on the other, of social and behavioural approaches to psychiatry, that the classical teachings of our European predecessors have seemed less and less important. *Topical Diagnosis in Neurology* will go far to redress the balance. Its author, Dr Duus, was trained by Kleist, himself a pupil of Wernicke, in Frankfurt. He is thus a representative of the main stream of this traditional German school of neurology. The book has been sensitively translated into English by Richard Lindenberg of Baltimore, also a graduate of the same German tradition. The text is economical, clear, and relevant, and altogether delightful to read. No attempt is made to stray from the primary intention of explaining signs and symptoms in neurology in relation to brain anatomy and physiology and the book is brilliantly illustrated with diagrams in two colours on almost every page. Both theoretical and practical aspects are discussed and well-chosen brief case reports provide pertinent examples of clinical problems. Even difficult areas, such as the thalamus and the disorders of higher function, receive a clear exposition, and the danger of over simplification is largely avoided. Not only are references to the older literature cited, but their historical context and current relevance are properly indicated. There are minor problems with the approach to certain aspects of clinical neurology, particularly the account given of the interconnections of the oculomotor nuclei in the brainstem, which does not take account of recent understanding of this neuro-ophthalmological system in terms of engineering approaches, but this sort of fine detail is not the primary intention of the book. This book fulfils its unique purpose admirably, providing information no longer readily available in the contemporary English literature and will be read with profit by senior and junior neurologists alike.

In *Neurology. A Textbook for Physicians and Students*, Professor Mumenthaler presents a didactic account of clinical neurology. The book is small in format but consists of more than 500 closely written pages. The plan of the book is conventional. Introductory chapters on clinical examination and special investigations are followed by chapters on diseases of the brain. These are described according to the traditional classification and ordered logically, but perhaps not entirely usefully, in systematic fashion. Thus, this part of the book begins with accounts of congenital and birth injuries and is followed by traumatic, neoplastic, infective, vascular, degenerative, hereditary, metabolic and 'other' types of neurological disease. A similar sequence is followed for disorders of the spinal cord. The organization of the book then seems to change direction so that the second half is occupied by autonomic and pain disorders, demyelinating disease, epilepsy, headache, and descriptions of cranial nerve disorders, spinal root disease, polyneuropathy and mononeuropathy, and myopathies. It is thus not always easy to use this book without recourse to the index and there is a certain amount of duplication between the two parts of the book. The writing itself is often somewhat opaque, partly because the translation uses idiosyncratic words, apparently derived from the German text (for example, serogenetic, paraspasticity, metaneoplastic, erythroprosopalgia), and partly because the content is not always in line with the current English and American practice, for instance, pneumoencephalography receives more emphasis than computed tomography. There are other problems that lead to difficulties and disagreement. For example, the discussion of headache implies that this symptom is common in hypertension without clearly specifying the accelerated phase of hypertension; the prognosis of multiple sclerosis is unduly gloomy and there are oddly placed facts within the text suggesting a loose policy during successive editions. Thus, the first paragraph of the section on epilepsy, headed 'Definition and causes' states that low IgA levels are found in patients with epilepsy. While this may be true, stated in a somewhat less definite form, this hardly seems the sort of information that should appear as an introductory concept in a discussion of epilepsy intended for students. Elsewhere in the book it is stated confidently that neurologists are frequently consulted about Scheuermann's disease. While this may reflect local practice in Berne this is certainly not a common cause of referral in London. The book suffers throughout from an excessive concern for detail and completeness that fits awkwardly in what is intended to be a pocket text. This second English edition represents a translation of the seventh German edition, originally published in 1982. It seems likely that the book has grown beyond its original intentions so that it now occupies an uneasy position between the comprehensive and the concise.

MICHAEL SWASH

Research Progress in Motor Neurone Disease. Edited by F. Clifford Rose (Progress in Neurology Series). 1984. Pp. 465. London: Pitman. Price £40.00.

The continuing proliferation of publications which report the proceedings of medical and scientific conferences or symposia is a phenomenon which continues to surprise and even to amaze. The number of such volumes to appear annually seems to increase steadily, even though the policy is continuously challenged by the innumerable reviews which question whether such publication is justified and by the trenchant views of the increasing numbers of congress participants who seek to oppose the semiautomatic request from the organizers for 'a manuscript'. This, all too often, results in the virtual duplication of material previously published. I have certainly been just as guilty as others, whether as author, editor or symposium organizer, and I venture to suggest that the same must apply to most of the older readers of *Brain*.

And so I turned to the pages of this latest publication to have stemmed from the seemingly inexhaustible, indefatigable and irrepressible editorial pen of Frank Rose with a feeling of some apprehension. It illustrates well some of the disadvantages and also some of the benefits which can be derived from this type of volume. As the editor says, this symposium, held in 1982, was substantially more productive and scientifically rewarding than the one which preceded it in 1976. Clinicians, epidemiologists, neuropathologists, neurobiologists, virologists and immunologists will all find something useful and important within its pages. And while we still do not have any clear indication of the fundamental processes involved in the aetiology and pathogenesis of this tragic, progressive disease, at least, as the contributions included here testify, we have a much clearer understanding of some of the processes involved in neuronal breakdown even if we know nothing of the trigger or triggers which initiate the disease process. It is good to note that the last four chapters deal with various aspects of the management of sufferers, though there is, of course, no mention, in a 1982 symposium, of the interesting and provocative studies of Engel and his colleagues (1983) on the role of thyrotropin-releasing hormone. The officers of the Motor Neurone Disease Association are to be congratulated upon their initiative in arranging the meeting and the editor should be thanked for presenting within the pages of a single volume a series of important and original contributions relating to this mysterious disease.

Inevitably there must be criticisms. The volume is by no means as up-to-date in a rapidly changing field as it would have been if it had appeared within a few months after the symposium. A publication delay of almost two years is unacceptable and in a book of this type I would feel that the absence of an index is also a major defect. Overall it contains less exciting new information on recent research progress and theories of pathogenesis than the succinct but comprehensive recent paper by Rowland (1984).

Hence this volume is no less, and no more than it claims to be. It is not a textbook; there are too many omissions from potential total coverage of what is known about the disease. It is not, in 1984, a comprehensive research review of 'the state of the art'. It represents simply the published proceedings of what must, for the participants, have been an enjoyable and fruitful symposium and most of the papers will repay study by those interested in this disease, even if there has been substantial progress since they were presented, and even though they are selective in their coverage.

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JOHN WALTON

Dementia: a Clinical Approach. By Jeffrey L. Cummings and D. Frank Benson. 1983. Pp. 416. Sevenoaks, Kent: Butterworth. Price £40.00.

This thorough-going treatise on dementia will doubtless achieve great success. It is notable for its clear and elegant presentation, wide range, and very detailed treatment of the many conditions giving rise to intellectual impairment. The text is supported by over 2,000 well chosen references to the literature and interspersed with valuable tables and illustrations. The result is a comprehensive production, pleasant to read and easy to delve into.

Clinical matters are the prime focus of attention but findings from laboratory research are incorporated where useful and appropriate. A refreshing and innovative aspect of the way the contents are ordered concerns the broad division into cortical and subcortical dementias. The former comprise Alzheimer's and Pick's disease, the latter Huntington's chorea and other dementias seen with extrapyramidal disorders and toxic-metabolic conditions. So firm a division perhaps transgresses finer points in the pathogenesis of these disorders but emphasizes an important new aspect of the conceptualization of dementia. The vascular dementias are accepted as illustrating both cortical and subcortical disease. All varieties of organic dementia are considered in great detail and a brief chapter describes the pseudodementias accompanying psychiatric disorders. Important sections deal *in extenso* with mental status evaluation and investigative aids towards diagnosis. The room for manœuvre in seeking out those conditions where treatment can be rewarding is amply illustrated.

Altogether this must be rated an outstandingly valuable and effective review of a fascinating segment of neurological and psychiatric practice.

W. A. LISHMAN

Aphasiology. Edited by André-Roch Lecours, François Lhermitte and Bonnie Bryans. 1983. Pp. 484. London: Ballière Tindall. Price £21.50.

This is a translation of Lecours and Lhermitte's 1978 French language volume, which was designed to inform not only neurologists, but the multidisciplinary audience of psychologists, speech pathologists, and linguists who engage in research and rehabilitation efforts in aphasia. The various chapters, which range widely over topics which are both central and peripheral to aphasia, have multiple authorship. Thirty collaborators from all the disciplines involved in the study and treatment of aphasia are listed, but Lecours is the principal author of more than half and a coauthor in all the chapters. In its size, and in the range of topics with which it deals in depth, this book is a fuller treatment of aphasia than any of the works published since Luria's (1970) *Traumatic Aphasia.* If it is not notable, like Luria's or Goldstein's works as a statement of an original theoretical position, it is on balance the best source in print for a thoughtful reconciliation of the many seemingly conflicting schools of thought on aphasia. It is also a work which does justice to the anatomical and physiological aspects as well as to the psychological and linguistic aspects of aphasia, with a rich supply of clinical case illustrations. Lecours' theoretical position and his engaging interpretative style provide an integrating thread through most of this book, without polemicism or dogmatism. Nevertheless, the inclusion of a number of chapters devoted to special topics related to aphasia introduces both a certain unevenness of quality and of purpose. The fact that this book was originally written for a French readership is occasionally intrusively evident, particularly in the chapter entitled 'Neurolinguistic Terminology', where French sources are almost exclusively cited for terms (e.g. 'syntagm') which do not translate into precise English equivalents, and where the speech samples used are French. Yet this same chapter includes a superb analysis and categorization of the psycholinguistic processes underlying the various forms of speech errors of aphasics.

One disappointing aspect of this book is that there is little evidence of updating of knowledge from 1978, except in the introduction to the English edition. Only a handful of references since 1976 appear, and these are all by the authors and collaborators While the accumulation of new knowledge in the field of aphasia is not dramatic, a number of recent developments, such as the recognition of the varieties of subcortical aphasia, are missing. Similarly lacking is any indication of the existence of computed tomography, on which the foregoing development is based.

One of the appealing aspects of this book is the historical and multidisciplinary perspective which begins with John Marshall's preface, the authors' introductions to the French and English editions, and the opening chapter on Historical Review. The strongest feature, however, is the comprehensive presentation of the clinical pictures of the various forms of aphasia. The authors wisely lead the reader into this section *via* a review of the deficits and positive symptoms which may be identified in the various syndromes, highlighting the psychological and linguistic factors which condition the form of their expression. The clinical illustrations offer a realistic guide to the range of variation which may be expected.

The integration of the clinical, anatomical, physiological, and neuropathological aspects of normal and aphasic language is undertaken in a long chapter on the Biology of Speech and Language. While this chapter begins with an introduction to the anatomical substrate of language for nonneurologists, it quickly moves into a historical review of concepts of the language zone, in terms of its structures and connections and how they may mediate linguistic processes. Detailed case studies of three typical forms of aphasia are presented in the form of clinicopathological exercises, illustrating how behavioural and neurological findings are integrated to lead to anatomical predictions and concluding with post-mortem findings.

The treatment of the typology of the aphasias is distributed across six chapters. While the experienced aphasiologist will probably recognize every form of disorder he knows under some heading in one of the chapters, the novice may find this organization confusing. For example, Chapter 4, titled 'Clinical Forms of Aphasia' presents the taxonomy espoused by the authors, which uses the terms 'Broca's', 'Conduction', Anomic', and 'Wernicke's' aphasia, the latter divided into three subtypes. Transcortical sensory aphasia is referred to as an alternative term for Wernicke's aphasia type II. Transcortical motor aphasia is not referred to until the chapter on frontal syndromes, where a disorder which the authors recognize as 'aspontaneity' is compared to both transcortical motor aphasia and to Luria's dynamic aphasia. In compensation, Chapter 10 on classification offers a review of problems of classification in historical perspective, with a fairly presented exposition of many authors' frameworks, from Baillarger to Goodglass.

The excellent chapters on language testing and therapy for aphasia deserve special mention, as they enhance the value of the book. Other chapters on special topics, such as aphasia in polyglots and language abnormalities in psychiatric patients deal with special research areas of the authors and their collaborators.

On balance, although uneven in quality, this is a valuable teaching resource, both as a textbook and a reference book. While its principal appeal is to newcomers to the field of aphasia, its contents are sufficiently rich to earn it a place in the library of those already well versed in behavioural neurology and aphasiology.

HAROLD GOODGLASS

Evoked Potentials in Clinical Medicine. By Keith H. Chiappa. 1984. Pp. 352. New York: Raven Press. Price $42.50.

Evoked Potential Manual. A Practical Guide to Clinical Applications. By E. Colon, S. Visser, J. de Weerd and A. Zonnefeldt. 1984. Pp. 342. The Hague: Martinus Nijhoff. Price Dfl. 140.00.

It has been the unfortunate fate of human evoked potential (EP) research that, after a number of years in which progress was slow but perceptible, the advent of real applications in the clinical field should have led to a flood of ill-conceived and poorly conducted investigations. The 'results' are frequently denied publication in scientific and medical journals, but find ready access to unrefereed proceedings volumes. First, therefore, let it be understood that neither of the books under consideration derives from a symposium or workshop, that both set out with the honourable intention of instructing neurologists, electrophysiologists and technicians in the basic principles of EPs, and that little else can be said in favour of the multiauthor volume.

With the minimum of assistance from one coauthor, Keith Chiappa assails the relevant technical, normative and interpretative aspects of *Evoked Potentials in Clinical Medicine* single-handedly. This confers the advantage of a consistent style which is concise and factual but never turgid. The standard of production is good and the price not excessive. When advising on the interpretation of records, a tendency to err on the side of conservatism is undoubtedly a fault in the right direction, but one could wish for less dogmatic insistence on stringent statistical criteria of abnormality. There are circumstances in which the correct identification of all abnormal cases at the expense of a significant proportion of 'false positives' may be more important than complete exclusion of the latter, and here a criterion of abnormality set at ±2 standard deviations from the normal mean may be more appropriate than the 3 standard deviations which Dr Chiappa considers mandatory.

The brainstem auditory EP, although probably the least widely applicable on account of the short length of the pathway concerned, is Dr Chiappa's chief area of expertise. Consequently, this section is the most satisfactory and can be whole-heartedly recommended as an exposition of factors affecting the normal response and the effects of disease. The chapters on the visual EP reflect the direction this field has taken over the past ten years, and therefore emphasize the pattern-shift (checkerboard reversal) technique to the virtual exclusion of other methods. This provides a useful introduction to the investigation as it has become established in clinical practice, but is unlikely to be a source of inspiration to those interested in future developments. In the last chapter devoted to the interpretation of somatosensory EPs one detects, perhaps, the influence of a looming deadline. The assistance of Con Yiannikas is required, covering lesions of peripheral nerve, brachial plexus and spinal cord, and here this reviewer was more gratified than scandalized that certain phrases had a familiar ring to them. Towards the end the treatment of degenerative conditions, cerebrovascular disease, epilepsy and many other complaints becomes cursory in the extreme, but the reference list is comprehensive of recent literature. It is in the SEP section that the one serious error of interpretation occurs. When the interval between cervical and cortical responses to a median nerve stimulus is increased, this is not necessarily due to a conduction defect above the level of the medulla (as Dr Chiappa asserts) since a considerable proportion of the cervical wave is generated in the root entry zone. The interval between a normal-looking cervical response and potentials arising in the cerebral cortex may, therefore, be increased when there is a lesion of the spinal cord above C6 level (as, for example, in spondylotic myelopathy).

Although the index is poor, animal literature is disregarded and no attempt is made to cover more esoteric responses such as those associated with performance of cognitive and motor tasks, Dr Chiappa's book can be recommended to all neophytes with interest in clinical problems. Not so the *Evoked Potential Manual* by E. Colon and colleagues, which epitomizes a second unfortunate trend in scientific book publishing. Here a major cost-cutting effort has been made such that, masquerading behind hard covers and a substantial price tag, we find the photographic reproduction of an ill-written (the English language is clearly not native to any of the authors), poorly laid out and indifferently illustrated typescript.

It is in the matter of content, however, that the deficiencies of this book become most apparent. The description 'manual' is probably intended as a disclaimer to any academic pretentions, and certainly the ground covered is much more limited than in other books so far published on this topic. However, to produce what is to be regarded as a textbook of the subject at relatively low level paradoxically requires greater expertise and judgement from the author than a 'state-of-the-art' survey of the literature. From the paucity and apparent arbitrariness of the published material chosen for illustration, it would appear that these authors are simply not familiar with the bulk of the literature. The practical advice is generally sound but the sample recordings are technically far from immaculate and lack all but the most rudimentary details of interpretation and clinical context. With so little investment of the publishers' faith, how can it be surprising that the returns are so low?

S. J. JONES

Computed Tomography of the Spine. Edited by Victor M. Haughton. 1983. Pp. 255. Edinburgh: Churchill Livingstone. Price £19.50 (soft cover).

It was clear from the early days of CT scanning that the transverse axial display of anatomy was particularly appropriate to spinal investigation, at least in those cases where a reasonably localized area of interest could be defined. The recent advances in scanner technology allowing high quality spinal images of narrow slice width, while maintaining contrast resolution, has led to very great interest in this application. A considerable quantity of work has now been published and the technique widely adopted particularly in North America where many institutions have now largely dispensed with more invasive techniques such as myelography.

This book is intended to provide a completely up-to-date account of CT investigation of the commonly encountered spinal pathologies. Seven of the eight chapters are produced by members of the Department of Radiology of the Medical College of Wisconsin in Milwaukee and an eighth chapter is written by a neurosurgeon who attempts to convey a clinician's perspective of the subject. A few illustrated case studies are included at the end of the book. The text of the book is well written and straightforward, there being little of a controversial nature in its description of these common pathological studies. As such the success of a book like this will depend largely on the quality of scan image reproduction and here there can be no criticism, the illustrated scans being of a very high quality and always showing the intended features.

Several texts devoted to spinal CT have now been published and, in fact, Professor Haughton, editor of this offering which is one of a series of volumes entitled *Contemporary Issues in CT*, was coauthor of an earlier and very good introductory text (Haughton and Williams, 1982). This current volume, however, is also a very sound introduction to the applications of CT in spinal disease and although its main readership will be found in radiological ranks it should make interesting and rewarding reading for all clinicians who may refer their patients for this form of investigation.

REFERENCE

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A. R. VALENTINE

Neurobiology of Cerebrospinal Fluid. Volume 2. Edited by J. H. Wood. 1983. Pp. 961. New York: Plenum Press. Price $89.50.

The end of the Introduction proclaims that CSF study is entering a new and exciting era. Almost 1,000 pages later one can easily subscribe to this notion, especially when one also notes that most of the references have been published within the past decade. There is broad scope not merely for the neurologist, but increasingly for the neurosurgeon and more recently for the psychiatrist.

Starting with solid chapters on the biochemistry, physiology and pharmacology of CSF, there are very practical clinical chapters on cancer therapy, infection and stroke. On the scientific side, the fundamental reasons for the new data are the more modern techniques of radioimmunoassay, autoradiography and monoclonal antibodies. These are a far cry from the old Pandy test.

Each chapter has been written by a practising expert in the particular field. The book complements and extends Volume 1 in the series, but leaves obvious gaps for a possible Volume 3. For example, there are useful clinical data on the role of CSF lactate in bacterial *versus* viral meningitis and the numbers of CSF proteins have recently been growing at a rather alarming rate.

The book is of value to the dedicated neurologist, neurosurgeon, psychiatrist and clinical pathologist as a major source for in depth coverage of what is clearly becoming a new growth phase in CSF studies.

E. J. THOMPSON

Parallel Processing in the Visual System. The Classification of Retinal Ganglion Cells and its Impact on the Neurobiology of Vision. By J. Stone. 1983. Pp. 438. New York: Plenum. Price $55.00.

For about twenty years Jonathan Stone has investigated the visual pathways, principally from the eye to the thalamus or midbrain in mammals and chiefly with anatomical methods. His long and detailed book is a testament to his unflagging enthusiasm, productivity and point of view. He is a man who cares—about unspoken assumptions in research, about considering all possible interpretations, about leaving no stone unturned, about studying as many species as possible. This can sometimes be tiresome, but the dedication and intellectual honesty shine through.

The book is in three parts. Part I reviews work on the classification of retinal ganglion cells carried out before 1966, summarizes a variety of evidence for three major types of ganglion cell in the cat (the familiar X, Y and W), then considers the position in animals for which there is much less evidence, namely monkey, rat, rabbit, tree shrew, goat, ground squirrel, frog, toad, pigeon, eel and mud-puppy. It is a clear and useful review of a complex topic. Part II is briefer, but the writing shows a passion absent from Part I. Here Dr Stone presents his views about the nature and pitfalls of classificatory methods, for example, feature extraction and parametric analysis of receptive fields; nominalism and realism; essentialism; testability and falsifiability; the unspoken influence of our ideas about Evolution. I have mixed feelings about Part II. For someone who has never thought about or encountered these things it may be useful and provocative, but I suspect that most readers are well aware of the issues he raises and some will even regard them as elementary. Dr Stone is right in saying that many assumptions underlie our classificatory methods. But most of us are so aware of them that we do not mention them in our reports, and that is the only sense in which the assumptions are hidden.

Part III is by far the longest section of the book. Apart from a consideration of the nasotemporal distinction in the retina, it leaves the eye and considers the evidence for the continuation of parallel processing in thalamus, midbrain and visual cortex. There are also chapters on the effects on the three main channels, and on vision, of various kinds of visual 'deprivation', on the relation between different visual channels and psychophysical performance, and on the evidence for parallel processing in other sensory systems. The first of these three chapters is comprehensive and illuminating, the second is brief and weakly argued and the third accurately reflects our relatively poor knowledge about the other systems. It might have been better to discard the last chapter and replace it with a notable absentee, namely a review of immunocytochemical work on different cell types, which has already provided important information in conjunction with other methods and is expanding rapidly and to some extent at their expense.

If I am less than entranced by the coverage of the book and by Dr Stone's overly didactic approach and conclusions, I have to confess to more than mild irritation at matters of style and presentation and interpretation. For someone with a professed interest in scholarship and erudition (*see* Preface) the style is unusual. For example, there are innumerable examples of the form 'A did this, B did this, C did this' and so on. Favourite words are 'seems', 'likely' and 'appears', which leave the reader wondering what the author really believes. Words are persistently used inappropriately, for instance 'guessed' for 'reasoned'. And rarely a page goes by without the deplorable tendency to string together nouns and use them adjectivally, for example 'the array of ganglion cells argument'. Some sentences are frankly slipshod, such as '... are Caldwell and Daw's (1978) Y/X/sluggish classification of rabbit ganglion cells and Rodieck's (1979) Y/X/ phasic/ tonic/ suppressed-by-contract/ direction-selective/ local edge detector/ color-coding classification of cat ganglion cells'. There are lots like this to amuse and bemuse the reader. The book is also over-illustrated. Many points in the text are perfectly clear without the necessity for full-page illustrations, from the original article, which are themselves difficult to follow because they are out of context. Moreover, a distressing number of errors have crept into the reproductions, namely, failure to label scales, arrows whose meaining is omitted, lettering that is not described. Finally, and it is not a trivial point, the development of our ideas about parallel processing is prominently but erroneously attributed to recent demonstrations that there are several different functional groups of retinal ganglion cells, whose outputs maintain the segregation. The idea of parallel processing in vision is much older, and stems from psychophysical experiments on human subjects and clinical investigations of neurological patients with highly selective visual impairments.

Despite its flaws, Dr Stone has written a book that is packed with information and has a clear theme. It is bound to rank with Polyak's *Vertebrate Visual System* and Rodieck's *The Vertebrate Retina* as a source of facts and ideas that will be widely consulted for many years. I never want to read it again from cover to cover but I shall be surprised if it does nor become one of my well-thumbed reference books on vision. There are precious few of these.

ALAN COWEY

Frontiers in Neuroendocrinology. Volume 8. Edited by L. Martini and W. F. Ganong. 1984. Pp. 305. New York: Raven Press. Price $57.50

This volume, like others in the series, contains a group of stimulating review articles which deal critically with some of the recent advances and controversies in neuroendocrinology. Much of this issue is concerned with the distribution and importance of peptide hormones. Three comprehensive articles, dealing with the urohypophysial hormones in teleost fish (Ledens) and the neuroendocrine regulation of satiety (Gibbs and Smith) and blood pressure (Reid and Schwartz) are included. In a further chapter (Le Roith and Roth) evidence for the existence of 'vertebrate peptides' in unicellular organisms and other invertebrates is reviewed. The fascinating concept that hormone secretion is not necessarily a function of highly specialized cells but one that may be performed by simple undifferentiated cells is considered, particularly with respect to hormone-secreting tumour cells and to the ubiquitous nature of peptides in the mammalian body. The distribution, assessed by immunocytochemical methods, of various regulatory peptides in the respiratory tract is discussed in a superbly illustrated contribution from Pollack and Bloom. Marked differences between diseased and healthy tissue are described which lead the authors to speculate that peptide messengers are involved in the aetiology of certain types of respiratory dysfunction and that drugs which modify their secretion or activity may ultimately be of therapeutic value. In the first of two articles on the hypothalamo-pituitary-gonadal system evidence for the involvement of catecholamines in the regulation of pulsatile (ultradian) LH secretion and in the midcycle gonadotrophin surge is catalogued exhaustively. Many of the current controversies are discussed but with surprisingly little regard to the limitations of the experimental techniques involved. In the other (Bex and Colbin) the complex physiological and pharmacological actions of LHRH are summarized. The use of the releasing hormone as a fertility drug is also considered briefly while the properties (chemical and pharmacological) and possible clinical uses of the superactive LHRH-receptor agonists and their antagonists are reviewed at length. The wealth of information contained in these two chapters is probably primarily of interest to specialists. Indeed, those with a lesser knowledge of the area may find the former difficult to follow as it contains a formidable number of abbreviations.

The remainder of the volume deals with interactions between steroid hormones and the nervous system. The intriguing evidence which suggests that dopamine contributes to the complex mechanisms which control aldosterone secretion is amply reviewed by Anguilara, while McEwan and his colleagues consider critically the mechanisms by which steroid hormones modify neurochemical transmission in discrete areas of the central nervous system.

The material presented in the eighth volume of *Frontiers in Neuroendocrinology* is undoubtedly of interest to scientists and clinicians concerned with the complex interactions of the nervous and endocrine systems. The comprehensive and readable nature of many of the articles should also make it a useful text for undergraduate students and for those with a more general interest in neurobiology.

J. C. BUCKINGHAM

Neuronal Development. Edited by Nicholas C. Spitzer. 1982. Pp. 424. New York and London: Plenum. Price $45.00.

The major questions of developmental neurobiology, clearly put by Spitzer in his useful foreword to this interesting collection of reviews, bear reiteration: 'How does the nervous system approach its differentiated state?', 'What is the cell lineage or mitotic ancestry of particular cells?', 'What are the relative contributions of the cytoplasm and its interaction with the genome, *versus* the contributions of the environment?' and finally 'What are the rules and the underlying molecular mechanisms that give rise to differentiated states, such as extended neurites or specific, stabilized synapses . . . ?'.

These questions have been addressed using a great variety of preparations. The leech, as reviewed by Stent, Weisblat, Blair and Zackson, has been particularly useful for studies of cell lineage because of its relatively simple nervous system with large, accessible, identifiable cells which can be injected with tracers, the distribution of which can then be followed through development. Goodman describes how cell lineage at somewhat later stages in development of the grasshopper has been examined by observing differentiation of specific cells at intervals of 1 to 2 per cent of embryonic life. Jacobson takes issue with the classical Spemann theory that the region dorsal to the blastopore of the developing amphibian acts as an 'organizer' of development of neural ectoderm, instead elaborating the theory of 'compartmentation' of neural precursor cells at the midblastula stage of development.

Monoclonal antibodies to cell surface components are likely to become important tools in sorting out cellular lineages. Barald reports how these have begun to be exploited in developing avian systems. Palka describes how genetic manipulation can be used to perturb and thus examine normal development of the nervous system in *Drosophila*. Influences on nerve fibre growth in tissue culture are described by Letourneau. Edwards discusses the importance of pioneer fibres in establishing pathways guiding growth of other fibres in the nervous system of the cricket. Mechanisms influencing synapse formation in the developing visual system of the branchiopod crustacean *Daphnia magna* are discussed by Flaster, Macagno and Schehr. The role of cell death in neuronal development is reviewed by Berg and the more parsimonious developmental process of synapse elimination, with emphasis on the neuromuscular junction, is discussed by Van Essen. Finally, Cowan and Finger provide a highly specialized account of regeneration in the chick optic tectum.

Normal development of the nervous system is an exquisitely orderly process. Perturbation of this process in man may be due to genetic error or to acquired malign influences on intrauterine development. A substantial part of paediatric neurology reflects such perturbations. This collection of reviews offers a useful introduction to the general area of nervous system development not only for the interested scientist, but also for the neurological clinician wishing to acquire some sense of current directions of research in developmental biology of the nervous system.

MICHAEL RASMINSKY

Neural Tissue Transplant Research. Edited by R. B Wallace and G. D. Das. Proceedings in Life Sciences. 1983. Pp. 260. Berlin: Springer. Price DM 108.00.

The field of neural tissue transplantation has made a dramatic resurgence in the past decade after being virtually dormant for fifty years. Much of the credit for renewed interest in transplantation to the central nervous system must be given to Björklund, Stenevi and colleagues in Sweden, and to Dr Das, one of the editors of the book under review. The exponential growth in the past five years of publications dealing with neural tissue transplants certainly warrants the publication of a text which critically reviews and makes some synthesis of the literature for the benefit of the many different neuroscience specialists being drawn to this field.

Neural Tissue Transplantation Research is composed of 8 chapters, and one is immediately aware from the contents pages onwards that the book is uneven. Articles range from as few as 9 pages to as long as 65 pages and there is little apparent virtue or merit in either extreme. Contributions from the editors, chapters 1, 3 and 8, comprise in excess of half the printed pages, and although there is some useful information in these chapters, there is also a lot of redundant material. The opening chapter by Das provides the reader with some useful insight and references to historical aspects of the field, but after this introduction the chapter proceeds on a laboured and repetitive course. Whilst the framework of this long chapter has been thoughtfully constructed in terms of important issues to be addressed, there is little substance to many of the subsections. The accompanying illustrations—tables, graphs and photomicrographs—do little to enhance the material.

Another significant portion of the book is given over to a chapter by Dr W. Kirsche on 'Matrix Zones' with special reference to regeneration in Teleosts, Amphibians and Reptiles. This otherwise excellent article seems strikingly out of place in the present volume, as only a small portion of Kirsche's material is addressed to neural tissue transplantation as such.

The book is certainly not without merit as chapters by Kromer, Dunnett *et al.* and Seiger provide well balanced reviews of their own contributions within the context of their individual fields of interest in neural tissue transplantation. The chapter by Kromer gives a good account of the successes with transplants in monaminergic and cholinergic systems. He discusses how adult PNS and embryonic CNS grafts have been skilfully used to probe the plasticity and regenerative capacity of the adult central nervous system, in terms of the ability of adult CNS to both give and receive new connections after injury. The article by Seiger highlights the advantages of transplantation to the anterior eye chamber, a versatile paradigm which is perhaps not fully exploited by researchers in this field. The chapter by Dunnett *et al.* illustrates how behavioural studies can be applied to assess the capacity of transplanted tissue to induce recovery after brain lesions. The authors skilfully demonstrate how anatomical and biochemical studies can be used to support results from behavioural testing, a combination of techniques that are perhaps all too rarely put together.

RONALD M. LINDSAY

Molecular Pathology of Muscle and Nerve. Noxious Agents and Genetic Lesions. Edited by A. D. Kidman, J. K. Tomkins, C. A. Morris and N. A. Cooper. 1983. Pp. 416. Clifton, New Jersey: Humana Press. Price $59.50 (hardback).

This book is based on the Third Symposium of the Foundation for Life Sciences held in Sydney, Australia, in February 1983. The theme was the investigation of the molecular pathology of nerve and muscle under a wide range of modifying influences which were either external agents or genetic defects. The symposium was subdivided into four sections comprising experimental neurology, toxic models of disease, behavioural neurology and muscle pathology. The topics covered were very wide-ranging, but the common ground throughout was the attempt to understand changes in more or less complex neuronal systems or in muscle in molecular terms, using naturally occurring or imposed perturbations as the investigative strategy. The interest is more probably for those working in the individual areas discussed rather than in the detection of any broad patterns that link the studies.

P. K. THOMAS

ERRATUM

Localization of function in the cerebral cortex: past, present and future. C. G. Phillips, S. Zeki and H. B. Barlow. *Brain*, **107**, 327.

The authors of this paper have requested that references to McKay (1974) should also have been inserted on p. 340, ll. 18 and 33.

FORTHCOMING EVENTS

Therapeutic and Psychological Aspects of Amyotrophic Lateral Sclerosis

An International Conference on this subject will be held in Varese, Italy, on March 29 to 31, 1985, organized by William T. Parlette, vice-president of the Amyotrophic Lateral Sclerosis Society of America and locally by Paolo Pinelli, Marco Poloni and Vittoria Cosi. Participation from neurologists and other physicians, nursing and therapy specialists, public health workers and staff and volunteers from ALS Societies is welcomed. The Conference will include a poster session. The cost will be approximately US $150.00.

For further information, contact Professor P. Pinelli or Professor M. Poloni, Neurological Clinic, University of Milan, Ospedale S. Paolo, Via Di Rudini 8, 20142 Milan, Professor V. Cosi, Neurological Clinic, University of Pavia, Via Palestro 3, 27100 Pavia, Italy, or Mr William Parlette, Postfach 51, CH 8932 Mettmenstetten, Switzerland.

Tenth International Meeting of the International Society for Neurochemistry

This meeting will be held in the Palazzo dei Congressi, Riva del Garda (on Lake Garda), Italy, on May 19 to 24, 1985. The deadline for the receipt of free communications (posters and oral presentations) is December 15, 1984. The official language will be English. Information concerning the scientific programme may be obtained from Professor G. Porcellati, Instituto di Biochemica, Universita di Perugia-Policlinico, Casella Postale 3-06100 Perugia, Italy. Telephone 049/810444, extension 404.

University of California, San Francisco: 18th Annual Symposium on Recent Advances in Neurology.

This postgraduate educational course will be held in the Fairmount Hotel, San Francisco, on February 13 to 15, 1985, and is designed for clinical neurologists, neurosurgeons and internists. Particular emphasis will be given to recent advances in the understanding of disease mechanisms and in patient management, including new concepts in the pathogenesis of cerebral infarction, Alzheimer's disease, Parkinson's disease, status epilepticus and thoracic outlet syndromes. Other topics covered will include toxic neuropathy, granulomatous angiitis, syncope, vertigo and stroke. Speakers will consist of members of the Department of Neurology, University of California School of Medicine at San Francisco with the following guest speakers: H. J. M. Barnett (University of Western Ontario), R. W. Gilliatt (Institute of Neurology, London), J. W. Langston (Stanford University) and J. Ochoa (University of Wisconsin).

The fee for practising physicians will be $295. Further information may be obtained from Extended Programs in Medical Education, Room 569-U, University of California, San Francisco, CA 94143, telephone 415-666-4251.

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OXFORD
AT THE CLARENDON PRESS

1984

Oxford University Press, Walton Street, Oxford OX2 6DP
London New York Toronto
Delhi Bombay Calcutta Madras Karachi
Kuala Lumpur Singapore Hong Kong Tokyo
Nairobi Dar es Salaam Cape Town
Melbourne Auckland
and associated companies in
Beirut Berlin Ibadan Mexico City Nicosia

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Printed in Great Britain
at the University Press, Oxford
by David Stanford
Printer to the University

BRAIN

A JOURNAL OF NEUROLOGY

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